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Office of Toxic Substances
Attn: Section 8(e) Coordinator (CAP Agreement)
Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Dear Sir or Madam:

Re: 8(e) CAP-0103; Data Submission

The enclosed document is submitted pursuant to the TSCA Section 8(e) Compliance Audit Program and the CAP Agreement between Rohm and Haas Company and the Environmental Protection Agency. This document does not contain confidential business information.

The following is a summary of the contents of the submission under Unit II.C.3 of the CAP Agreement:

Tested Chemical:	Oxirane
CASRN:	75-21-8
Title of Report or Study:	Final Report, Ethylene Oxide, Two-Year Inhalation Study on Rats (Report No. 81RN-1005)
Reportable Effect:	Increased tumors.

If additional information is required, please contact the undersigned at (215) 592-3139. Thank you.

Sincerely,

Ronald L. Keener

Ronald L. Keener, Ph.D.
Regulatory Affairs Director
Product Integrity Department

RLK:so
Enclosure

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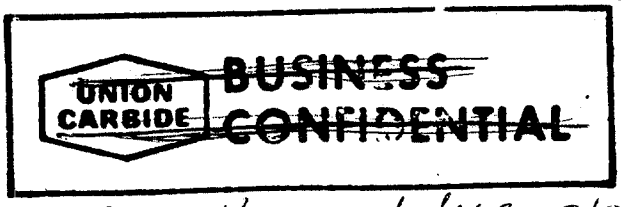
81RN-1005



R. L. Keener / SMG 8/26/92

44-20

FINAL REPORT

ETHYLENE OXIDE

TWO-YEAR INHALATION STUDY ON RATS

JANUARY 28, 1981

BUSHY RUN RESEARCH CENTER
4400 FIFTH AVENUE
PITTSBURGH, PA 15213

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Bushy Run Research Center
A Joint Mellon Institute - Union Carbide Corporation Operation

ETHYLENE OXIDE INTER-COMPANY TOXICOLOGY PROGRAM

The research program herein reported was monitored on behalf of the joint industry co-sponsoring participants by a Steering Committee comprised of representatives of the following companies:

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ABSTRACT

Fischer 344 rats were exposed to 100, 33 or 10 ppm of ethylene oxide vapor (EO) by the inhalation route for 6 hours per day, 5 days per week for approximately two years. Two air control groups were exposed under similar conditions. Whole body exposures were conducted in a dynamic exposure system where the vapor concentration levels were determined by gas chromatography. Initially, 120 rats per sex per group were exposed, and at each 6-month interval a portion of the animals was sacrificed to determine possible treatment-related effects. Interim evaluations included hematology, serum clinical chemistry, urinalysis, body weight, organ weight, bone marrow cytogenetic, and gross and histologic examinations.

Under the exposure conditions of the study, inhalation of EO resulted for one or both sexes in a depression of body weight gain and an increase in mortality at 100 and at 33 ppm of EO but not at the 10 ppm level. At the 6-, 12-, and 18-month sacrifice intervals, there were no consistent patterns of association of any alteration in urinalysis or hematology or serum clinical chemistry or organ weight with histologically confirmed organ damage. However, a slight depression in erythrocyte count and hemoglobin value in the female rats of the 100 ppm group was noted after 12 months. Skeletal muscle atrophy was present in the 100 ppm exposure group at the final sacrifice interval.

At the final sacrifice interval, histologic findings confirmed hematologic evidence that exposure to EO resulted in an increased prevalence of mononuclear cell leukemia. The prevalence of this neoplasm in the females was dosage-related and increased for each of the three exposure concentrations. The prevalence of other neoplasms was increased as demonstrated by the greater number of rats with more than 2 neoplasms; this was noted also in each of the three exposure concentrations for the female rats. Furthermore, in both the 100 and 33 ppm exposure groups, the number of female rats with malignant neoplasms was increased. The frequency of peritoneal mesothelioma was treatment-related in the male rats exposed to 100 or 33 ppm of EO. The normal incidence of pituitary adenoma appeared to be accelerated in the female rats exposed to 100 ppm of EO. While the incidences of mononuclear cell leukemia, peritoneal mesothelioma and pituitary adenoma in the air control rats were similar to those reported in the literature, the possible contribution of any interaction between EO exposure and sialodacryloadenitis viral outbreak (during the 15th exposure month) is unknown.

To conclude, biologically significant adverse effects were observed at all concentrations tested.

METHODS

Test Material

The test material, liquid ethylene oxide (CAS No. 75-21-8), that was used for the entire study, was received from Union Carbide Corporation (UCC) on April 25, 1977 with a UCC identification number 7JNC45,G581. This material was assigned the Chemical Hygiene Fellowship (CHF) Sample Number 40-163. The liquid ethylene oxide (EO) was contained in a 55-gallon drum, which had been filled from a tank car (#GATX84731) loaded with refined ethylene oxide. The production site of the EO was Union Carbide Corporation, Seadrift, Texas.

Liquid Ethylene Oxide Chemical Analysis

Based on initial chemical analyses, it was determined by Union Carbide Corporation that the test material was representative of UCC commercial grade ethylene oxide.

Liquid ethylene oxide was chemically analyzed periodically during the study at the Research and Development Department, UCC, South Charleston, West Virginia. The UCC maximum commercial specifications and results of the chemical analyses of the test material are presented in Table 1. Other than the water content of the samples, dated March 31, 1976 and April 23, 1977, all analyses were within the maximum commercial specifications throughout the entire study.

At the initiation of the study, the chloride content of the ethylene oxide was measured by UCC at the Institute Plant Laboratory, South Charleston, West Virginia, Table 2. The organic chloride compounds were identified as ethyl chloride, ethylene chlorohydrin, ethylene dichloride and vinyl chloride. These organic compounds were identified by gas liquid chromatography. The chloride content of each compound was calculated. The total of these calculated values, 10.1 ppm, agreed with the total chloride content, 10.1 ppm, of the EO as determined by a Dohrmann Chloride Analyzer.

Ethylene Oxide Sample Storage

The storage drum in which the EO was shipped was kept in a sheltered area outdoors for the duration of the study. An aliquot from the storage drum (approximately 5 lbs) was transferred to a stainless steel cylinder by using nitrogen gas pressure to force the liquid through the stainless steel connecting lines. The cylinder was then attached to the generation system.

Ethylene Oxide Vapor Generation

The stainless steel cylinder containing EO was maintained at approximately 35°C by means of a constant temperature bath. The EO vapor pressure at that temperature was utilized to move the gas through a stainless steel gas line and a pressure-reducing regulator. Manifolds of stainless steel tubing directed the vapor from the gas line through a control valve and a flowmeter to the chamber air-inlet duct. There, EO was diluted and mixed with room air and drawn into the respective inhalation chambers. At the end of each exposure day, the gas line and manifold system were purged with nitrogen gas.

Table 1
Chemical Analysis and Specifications for Ethylene Oxide[1]
Used During the 2-Year Inhalation Study

Chemical Analysis	Analysis Date						Maximum Commercial Specifications[2]
	Mar 31, 1976	Apr 23, 1977[3]	Apr 20, 1978	Jul 18, 1978	Dec 8, 1978	Nov 14, 1979	
Acidity (% by wt.)[4]	0.0009	0.0016	0.0020	0.0014	0.0014	0.0016	0.0020
Aldehydes (% by wt.)[5]	14	21	12	19	30	15	30
Acetylene (ppm)	none	none	none	none	none	none	none
Water (% by wt.)	0.06	0.05	0.001	0.005	0.01	0.018	0.03
Residue (g/100 ml)	0.0004	0.0012	0.0018	0.0004	0.003	0.0004	0.005
Color (Pt-Co)[6]	3	3	1	1	1	1	10
Odor	nonresidual	nonresidual	nonresidual	nonresidual	nonresidual	nonresidual	nonresidual
Suspended matter	SF[7]	SF	SF	SF	SF	SF	SF

[1]CHF Test Sample #40-163 (UCC reference #7JNC-45,G581).

[2]Commercial specifications of Union Carbide Corporation.

[3]Maximum of two analyses.

[4]Measured as acetic acid.

[5]Measured as acetaldehyde.

[6]Platinum - cobalt color test.

[7]SF - Substantially Free.

Table 2
Chloride Content of Liquid Ethylene Oxide Used in the 2-Year Inhalation Study

Material	Organic Chloride Content[1] (ppm, w/v)[2]	Calculated Chloride Content (ppm Cl^-, w/v)[2]
Organic Compound		
Ethyl chloride	12.2	6.7
Ethylene chlorohydrin	3	1.3
Ethylene dichloride	2	1.4
Vinyl chloride	1.3	0.73

[1]Determined by gas liquid chromatography (glc)

[2]To convert from w/v to v/v: multiply by reciprocal of the density of the organic chloride at 20°C, i.e.,

$$(\text{w/v value}) \times \frac{1}{\text{density at } 20^\circ\text{C}} = (\text{v/v value})$$

WPC/1080-7

Inhalation Chamber Room

All chambers were located in Room No. 138. Presented in Figure 1 is a schematic of this room showing the chambers and generation system. The animals were exposed in the chambers during the day and were kept in this same room overnight. No EO could be detected by gas chromatography in the exposure room when all animals were removed from the chambers. Even in the room space adjacent to the 100 ppm animal cage carriers, no EO could be detected after exposure.

Inhalation Exposure Chambers

Five identical chambers, rectangular in shape, each had a volume of approximately 3800 liters with internal dimensions of 2.1 meters long, 2.0 meters high and 0.9 meters wide. The chambers were stainless steel-lined and contained glass windows for animal observation. Inside each chamber, a delivery duct, with holes equidistantly spaced, was mounted on one of the walls and extended lengthwise along the top. An identical duct for chamber exhaust was located near the floor of the chamber directly beneath the inlet duct. Artificial light from the room was the only source of light in the inhalation chamber. Each chamber held two carriers with animal cages.

Ethylene Oxide Vapor Distribution and Temperature Variation Within Inhalation Chambers

During a preliminary study in which rats were exposed in the chamber, a multi-point analysis of the chamber atmosphere for EO was performed. The results of the chemical distribution (Appendix I, Table A-1) indicated that the generation/exposure system produced an atmosphere containing EO in the breathing zone of all animals that was approximately $\pm$ 7% of the mean concentration for all the sampling points within the chamber and could be reproduced daily. Each point where temperature was measured within the chamber did not vary by more than approximately $\pm$ 11% from the mean of all points (Appendix I, Table A-2). Hence, during the exposure, the chamber atmosphere was sampled for EO from the middle of the chamber, between the two animal cage carriers; the chamber temperature and humidity were determined near the front of the chamber. Both locations were representative of the areas in which animals were placed.

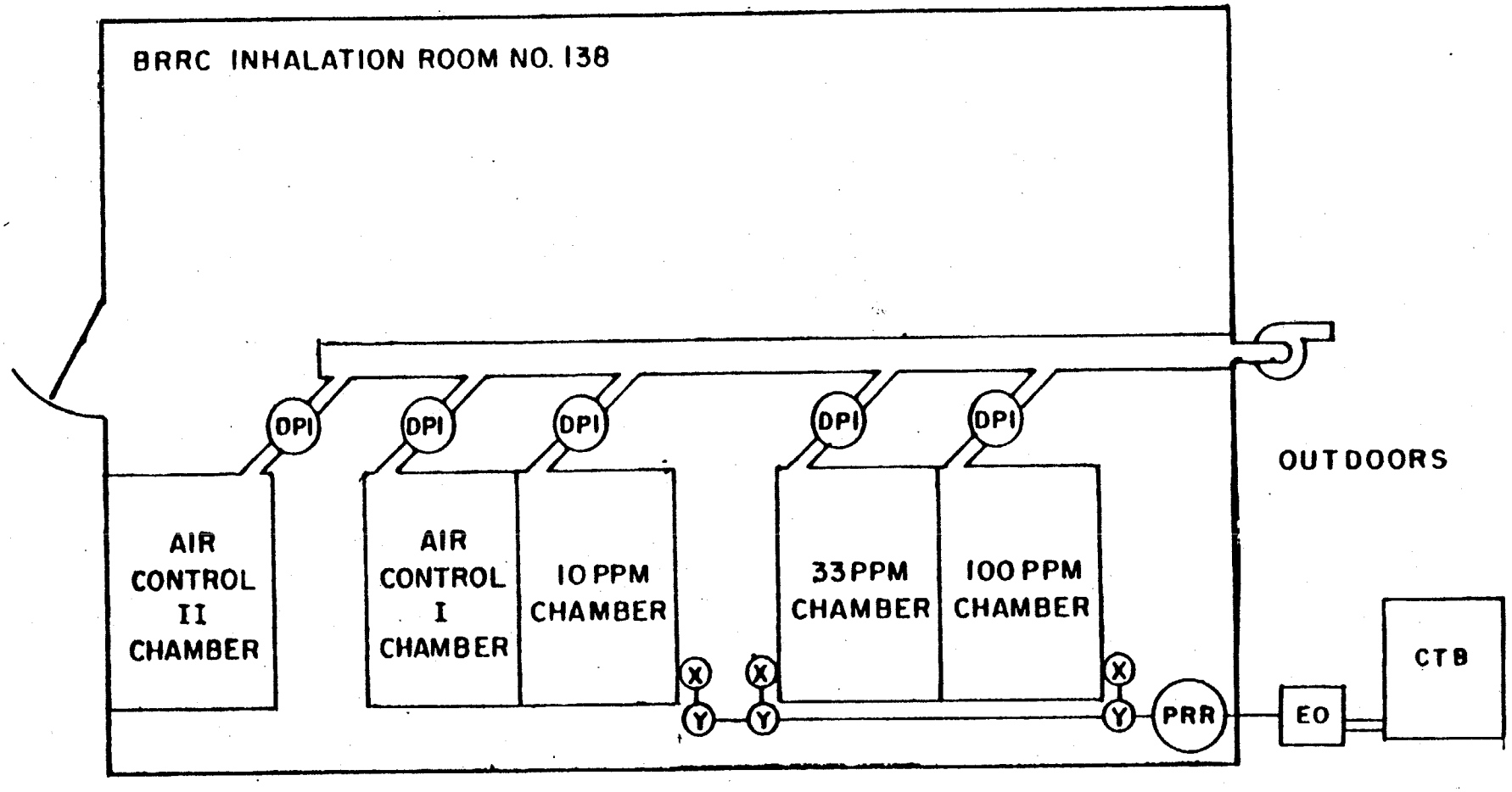
Chamber Airflow

In a preliminary study, it was found that a chamber airflow of approximately 3,000 liters per minute (approximately 47 air changes per hour) adequately reduced, in all areas of the chamber, the temperature which was caused by the body temperature of the animals.

Recording of Chamber Temperature, Humidity and Airflow Rate

During each 6-hour exposure, chamber temperature, relative humidity and airflow rate were recorded approximately 5 times a day.

Figure 1



DPI – Differential Pressure Indicator for determining chamber airflow

(X) – Air intake with Jet for introduction of EO

(Y) – EO Flowmeter for measurement of flow from manifold line into chamber

PRR – Pressure Reducing Regulator

EO – EO contained in a stainless steel cylinder which is connected to manifold line

CTB – Constant Temperature Bath

– Chamber Exhaust Pump

Ethylene Oxide Vapor Concentration Determination

All chambers, including both control chambers, were monitored for EO concentration by means of a Perkin Elmer 3920B gas chromatograph (GC). Pertinent information regarding the operating conditions of the GC is presented in Appendix I, Table A-3. An automatic sampling and recording system connected to the GC acquired the sample and recorded the data on a printer and on magnetic tape. A known primary standard concentration of ethylene oxide was sampled several times before the start of daily chamber analysis to check the monitoring system. Furthermore, during each cycle of chamber analyses, the same standard was re-analyzed. Approximately 7 samples were analyzed from each chamber each day. Conversion of part per million, ppm (expressed as volume/volume), to mg/M^3 is 1 ppm = 1.8 mg/M^3 (25°C and 760 mm Hg).

Selection of Target Chamber Concentrations

The goal of the study was to establish the concentration levels which would result in a no ill-effect level and a minimum-effect level. The minimum-effect level is one which is expected to result in some significant biological effect, such as reduced body weight change, but to have minimal or no effect on the life span of the animals.

It was agreed by the Ethylene Oxide Steering Committee that the EO exposure levels would be 100, 33 and 10 ppm of EO. Justifications for these exposure levels are as follows:

High-EO-Concentration Level: In a preliminary inhalation study at this laboratory, it was observed that 8 weeks of exposure to either 150 or 100 ppm of EO resulted in statistically significant reduction of body weight change in male and female Fischer 344 rats. These data agreed with the results of a 6-month inhalation study on rats performed by Hollingsworth, et al., 1956.

Also noted during the 8-week exposure to 150 ppm of EO in male and female rats were statistical differences in hemoglobin concentration and in kidney weight expressed as a percentage of body weight. This was not observed at the lower concentration levels of 100 or 50 ppm. Even though there were no deaths in the 150 ppm exposure level, because of the degree of depression of body weight gain (i.e., when compared to the control, male body weight gain was depressed 16% and female weight gain was depressed 29%), it was judged that the survival rate at 150 ppm exposure would be significantly affected in the chronic study. Hollingsworth, et al., reported that an appreciable number of rats died during 6 months of exposure to 204 ppm of EO, but no deaths were reported for 6 months of exposure to 113 ppm of EO. Consequently, 100 ppm of EO was chosen as the high-concentration level for the chronic study.

Intermediate-EO-Concentration Level: Based on unanswered questions raised by particular regulatory agencies on the health safety of EO inhalation exposure, it was felt that the Threshold Limit Value of 50 ppm (TLVs®. Threshold Limit Values for Chemical Substances in Workroom Air Adopted by American Conference of Governmental Industrial Hygienists, 1976) might be lowered in the future. Consequently, the intermediate-concentration level was chosen to be 33 ppm, 1/3 of the high-concentration level.

Low-EO-Concentration Level: Based on preliminary experiments, it was believed that an exposure concentration below 10 ppm would be difficult to maintain at a stable level throughout the study. Therefore, 10 ppm, 1/10 of the high-concentration level, was selected as the low-concentration level.

Air Control Groups: It was decided that two separate groups of animals would be subjected to the same inhalation exposure regimen as the EO-treated animals, but these animals would be exposed to room air only. These two groups would serve as independent air-control groups. The purpose of having two control groups was to allow for better assessment of the variability in this study between non-chemically treated groups of animals.

Exposure Regimen

Animals were exposed to room air or ethylene oxide vapor for 6 hours a day, 5 days a week for approximately 2 years. The first exposure was on April 27, 1977, and the last exposure was on June 6, 1979, for a total of 525 exposures. The 4 days in April, 1977 (April 27 through 30) together with the whole month of May were considered the first exposure month. The duration of all subsequent exposure months was based on the calendar month. There was a total of approximately 25 exposure months before the study was terminated. The only extended non-exposure period during this study was for two weeks. This occurred in the 15th exposure month during the acute clinical phase of a virus infection (Refer to section in the Results on Sialodacryoadenitis Virus Infection). All other interruptions in exposure were for short periods of time (approximately one day or less) and were because of a national holiday or an equipment failure.

Exposure to the vapor began each day at approximately 7:30 a.m.; the flow of ethylene oxide was shut off at the chamber 6 hours later. The animals were then left in the chamber for at least 30 minutes before they were removed.

Animals

Fischer 344 rats (F344/Mai fBR), which is an inbred strain, were obtained from Microbiological Associates, Walkersville, Maryland. These animals were barrier sustained, Caesarian originated. The shipment of rats was transported to this laboratory in an environmentally controlled truck which arrived on April 13, 1977.

Quality Control: Immediately upon arrival and during a 2-week quarantine period, the general health status of the rats in the shipment was assessed by evaluating 5 male and 5 female rats which were randomly selected. The following parameters were evaluated: feces for intestinal parasites; nasal pharynx and lung for aerobic bacteriologic flora; blood for viral antibodies and parasites; and urine for urinary tract parasites. Furthermore, blood hematologic and clinical chemistry determinations, urinalysis, ophthalmologic examinations, gross necropsy and histopathologic examinations were performed. The findings of the quality control examinations were within usual limits for commercially available specific pathogen-free rats and, therefore, the rats were determined to be of suitable quality for the long-term inhalation study.

Animal Identification: All animals were individually numbered by using combined toe-clipping and ear-notching methods. Each animal of the same sex was given a different number. Listed on each cage card were the identification numbers for the animals within the cage. Each exposure group had cage cards that were color-coded to indicate the exposure concentration.

Group Assignment and Number of Animals per Group: Before random selection of the rats into groups, all animals were weighed at least 3 times. Animals were removed from the stock group if the rat was not gaining weight normally, if abnormal clinical observations were noted, or if the body weight at the time of the random selection into groups was above or below two standard deviations from the mean for all animals of that sex.

Each group contained 120 rats of each sex, making a total of 240 rats per level or 1200 rats for the entire study. The groups were designated and will be named in this report as follows: 100 ppm group, 33 ppm group, 10 ppm group, Air Control I (also indicated as CI, 0-I or 0 ppm-I) and Air Control II (CII, 0-II or 0 ppm-II). In addition, a group of male and female rats was retained to be used for subsequent cytogenetic studies.

Animal Husbandry

Food and Water: During the non-exposure period, Wayne Lab-Blox F-6® feed, Allied Mills, Inc., Chicago, Illinois, and water were available ad libitum. All feed was removed from the cage, and tap water was drained from the water system of the cage carriers before each exposure.

Lighting, Temperature and Relative Humidity: The artificial fluorescent lighting was on a 12-hour light and 12-hour dark cycle (approximately 5:30 a.m. to 5:30 p.m.). When the animals were in the room, the temperature and humidity controlling devices of the non-recirculated air supply to the room were set to maintain the environment between 68 and 72°F and 40 to 60% relative humidity.

Caging and Rotation of the Cages: Animals were housed 5 rats per sex per cage. The dimension of each stainless steel wire mesh cage was approximately 15 inches wide, 14 inches deep and 7 inches tall. These cages were kept on stainless steel animal cage carriers. The rats were housed in the same cages during exposure and non-exposure periods.

A stainless steel shelf pan was placed between each level of cages to prevent urinary and fecal contamination of animals on lower tiers. These pans were in place during the exposures. After each exposure, clean pans with absorbent paperboard (Deotized Animal Cageboard®, The Upjohn Co., Kalamazoo, Michigan) were placed on the carriers. Before exposure, the absorbent paperboard was removed.

To equalize any minor differences within the chamber even though undetected in environment or concentration of ethylene oxide, all cage positions were rotated on a weekly basis. At the time of rotation, the animals were transferred to clean cages and animal cage carriers.

Observations and In-Life Laboratory Studies

Animal Observations: During the six-hour exposure, a portion of the animals was observed several times daily through the chamber windows. However, most changes in general health status were better observed for all animals immediately before and after the exposure. At each weekly transfer of the animals to clean cages and at each weighing and palpation interval, significant changes in health status were also noted.

Once a month, a more in-depth observation and recorded frequency table of clinical observations were made on 20 rats of each sex from the 100 ppm group and 10 rats of each sex from each of the two air control groups. These rats were randomly selected, and the same ones were followed throughout the study. Special attention in this monthly in-depth clinical observation was given to noting the possible presence of the toxicologic effects previously reported by Hollingsworth, et al., 1956 and Jacobson, 1956. The monthly examination included the evaluation of the presence of the following: reddish-brown fur around the neck, pilo-erection, emaciation, lacrimation, salivation, nasal discharge, conjunctivitis, soft stool, hypopnea, dyspnea, apnea, kyphosis, ataxia, abnormal muscle contractions, abnormal hind-quarters lift reflex, abnormal righting reflex, irritable behavior and hypoactivity.

Body Weight Determinations: All animals were weighed the day before the first exposure. This weight was considered the pre-exposure reference weight and was subtracted from each subsequent weight determination to obtain a change in body weight value. Body weights were measured weekly through the first 3 months of exposure, every 2 weeks from 3 through 6 months and monthly thereafter.

Palpation for Abnormal Tissue Masses: At each body weight determination interval, all animals were visually examined for abnormal tissue masses. From the 12th exposure month to the end of the study, all rats were given a more in-depth examination, including palpation at monthly intervals.

Ophthalmologic Examination: Prior to each sacrifice interval, the animals to be sacrificed were examined with the use of an indirect ophthalmoscope. Dr. Roy W. Bellhorn, D.V.M., a veterinary ophthalmologist, was the examiner at each observation interval. All observations were performed immediately following an exposure. One drop of a mydriatic, Mydriacil®, 0.5 percent, (Alcon Laboratories, Inc., Fort Worth, Texas) was instilled in each eye prior to examination.

Sampling Frequency and Number of Animals for Urinalysis, Hematology, Blood Coagulation Time Determination and Serum Clinical Chemistry: The appropriate biological samples for each examination were collected from the animals to be sacrificed before each of the scheduled necropsy intervals. The number of rats sampled for each examination was 10, 10, 20 and 20 per sex per group for the 6-, 12-, 18- and 24-month sacrifice intervals, respectively. [Note: Blood coagulation time determination was not performed at the final sacrifice interval.]

Urine Collection and Urinalysis: At approximately 6:00 a.m., the animals were placed one per cage in metabolism cages for urine collection. Urine was collected for approximately 1.5 hours. The samples were not pooled.

The following parameters were determined in the routine urinalysis by using a dipstick method of analysis (N-Multistix®, Ames Division, Miles Laboratories, Inc., Elkhart, Indiana): pH, protein, glucose, ketone, bilirubin, occult blood, nitrite and urobilinogen. The color, turbidity and volume were recorded, and specific gravity was determined using a refractometer. Meaningful volumetric data could not be obtained because of the short collection period.

For the microscopic examination of urine sediment, all significant findings, including identification of certain types of crystals, cells and microorganisms, were recorded.

Blood Sample Collection: Immediately following urine collection, the same animals were lightly anesthetized by the inhalation of methoxyfluorane (Metophane®, Pitman-Moore, Inc., Washington Crossing, New Jersey). Blood was obtained from the retro-orbital sinus by the use of a capillary tube. One drop of blood was placed on a microscope slide for determination of blood coagulation time. The blood sample collected for hematologic evaluation contained ethylenediaminetetraacetic acid (Vacutainers®, Becton-Dickinson, Rutherford, New Jersey). The blood sample collected for clinical chemistry was allowed to clot. The serum was submitted for analysis. All blood samples were collected within two hours and promptly analyzed.

Hematologic Evaluation: Blood samples were submitted for the following routine hematologic determinations using a Coulter Counter (Model ZBI)®: red blood cell count, mean corpuscular volume, hematocrit, hemoglobin and total white cell count. Mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration were calculated from the above data. The white blood cell differential counts were manually obtained by microscopically identifying 100 leukocytes in a stained blood smear. The appropriate samples were taken and saved for future possible evaluation of reticulocyte count and bone marrow smear differential count.

Blood Coagulation Time Determination: Immediately after collecting a drop of blood on a cleaned microscope slide, a needle was passed through the drop until fibrin strands were observed. The time of first appearance of the fibrin strands was recorded.

Serum Clinical Chemistry: The following analyses were performed on a Centrifichem 300F® (Union Carbide Corporation): hydroxybutyric dehydrogenase, alkaline phosphatase, creatine phosphokinase, lactic dehydrogenase, aspartate aminotransferase, alanine aminotransferase, calcium, glucose, urea nitrogen, creatinine, cholinesterase, total protein, albumin, hemoglobin, gamma glutamyltransferase and total bilirubin. Hemoglobin concentration of the serum was determined to indicate the possible degree of hemolysis.

Cytogenetic Studies

Microscopic examination of chromosomes for quantification of chromosomal aberrations was performed on a portion of the animals that were submitted for necropsy at the 6-and 12-month sacrifice intervals. Slides were prepared from 10 rats per sex (and 5 rats per sex from a positive control) at the 18-month sacrifice interval for possible future studies if warranted.

Chromosome preparations were made from the bone marrow of the left femur of sacrificed rats in Air Control groups I and II, a group injected with triethylenemelamine (served as positive control), and from the the animals exposed to the three respective concentrations of ethylene oxide. An attempt was made to examine the chromosomes of 50 cells per rat, from 10 rats per sex exposed to 100 ppm of ethylene oxide, 5 rats per sex in each air-control group and from the positive control group. Detailed methods for these studies are outlined in the Standard Methods section of Appendix IV.

Necropsy

Ten rats per sex per level were necropsied at the 6- and 12-month sacrifice intervals and twenty rats per sex per level at the 18-month interval. All remaining rats were necropsied at the final sacrifice. All rats to be necropsied were anesthetized with methoxyfluorane and sacrificed by exsanguination. Because of the number of animals and the extensive laboratory testing and necropsy procedures, not all animals of one sex could be sacrificed within one day. To lessen the chances of day-to-day biological or experimental variablity from biasing the results, the same number of randomly selected animals per sex from each group was sacrificed each day, when possible. The order in which the animals were bled and sacrificed is the same order in which the data are presented in each table, so that day-to-day variation, if present, could be detected. Furthermore, to lessen the chances of adding another possible variable (recovery) into the evaluation, each scheduled sacrifice began after two consecutive daily exposure periods. The only exception to this was the final sacrifice.

A complete gross dissection and evaluation were performed on each sacrificed animal and on all animals which were found dead or moribund. The following organs were weighed from the scheduled sacrificed animals: liver, kidneys, spleen, adrenals, brain and testes (right and left separately).

Histopathologic Examination

Tissues were fixed in 10% neutral buffered formalin. The required tissues were processed, sectioned and stained with hematoxylin and eosin for histopathologic examination. Refer to the histopathologic reports in the Appendix for a listing of what tissues were examined and for a thorough description of the procedures followed for each scheduled and non-scheduled (dead and moribund animals) sacrifice interval.

At the 6-month necropsy interval, histopathologic examination was performed on all tissues of the rats of each air-control and the 100 ppm group. At the 12- and 18-month necropsy intervals, histopathologic examination was performed on selected organs, and on any tissue with gross lesions from rats of each control group and from the 100 ppm group. Histopathologic examination of rats of the two lower exposure groups was performed on any tissue with gross lesions at the 6-, 12- or 18-month periods.

At the 24-month necropsy interval, histopathologic examination was performed on all tissues of rats in the 100 ppm and both control groups and on potential target tissues, selected tissues, and tissues with gross lesions in the 33 and 10 ppm groups.

Randomization

All assignment of animals into exposure groups was accomplished by the use of a computer-generated random number scheme. All of the selections, e.g. for in-life examinations or for sacrifice, were accomplished by a stratified randomization selection technique using a card-based randomization number scheme. This procedure prevented the chance occurrence that too many animals would be selected from the same cage or from the same location within the chamber.

Statistical Procedures

The results of quantitative continuous variables were intercompared among the three concentration levels and two control groups by use of analysis of variance, Bartlett's homogeneity of variance (Sokal and Rohlf, 1969) and Duncan's multiple range test (Duncan, 1955; Duncan, 1957; Harter, 1960). The latter was used when F for analysis of variance was significantly high ($p < 0.05$, two-tailed), to statistically compare each exposure group to each air control group separately and to intercompare the two air control groups (these comparisons were also made for the following methods, when appropriate). If Bartlett's test indicated heterogeneous variances, the F-test (Sokal and Rohlf, 1969) was used for each exposure group versus the controls and to intercompare the variances of the controls. If the F-test was not significant, Student's t-test (Sokal and Rohlf, 1969) was used to compare the means; if the F-test was significant, the Cochran t-test (Cochran and Cox, 1957) was used. In addition, mortality and tumor-incidence data of the EO-exposed groups were compared to the combined data of the two control groups.

Contingency and appropriate non-parametric data were compared employing a multiple comparison test, such as an R x C chi square (Sokal and Rohlf, 1969). Fisher's exact test (Sokal and Rohlf, 1969) was used if R x C chi square was significant or if chi square was inappropriate because of the occurrence of too many low expected frequencies.

For certain urinalysis, clinical chemistry and hematologic parameters, neither parametric nor non-parametric statistical comparisons were applicable. The data were not continuous and, in ranking, there were very many tied values. The parameters for which no statistical comparisons were performed are indicated in each summary table, and the medians and quartile deviations are reported (Sokal and Rohlf, 1969).

Mortality was compared by the life table method of Cutler and Ederer (1958), while the McKinney et al., (1968) life table procedure was used for the tumor incidence data. For the mortality and tumor data, the critical ratios (Garrett, 1967) were compared using standard errors described by Cutler and Ederer. Other

statistical methods will be referred to in the section "Frequency of Neoplasms That Were Determined to be Potentially Treatment-Related". The probabilities associated with the critical ratios or the results of the Fisher's exact comparisons for mortality, for histologic lesions, and for tumor incidences were adjusted to account for the multiplicity of tests by the Bonferroni correction (Gart et al., 1979). As therein stated, for r doses (or comparisons to the control groups), the Bonferroni correction requires that the computed p be adjusted so that significance is claimed only if p is less than α/r for an overall α error rate. Examples follow:

α	Each of Three Treatment Groups Compared to: Each Control $\alpha/6$	Each of Three Treatment Groups Compared to: Combined Controls $\alpha/3$	One Control Compared to the Other Control α
a = $0.05 > p > 0.01$	0.00833	0.0167	0.05
b = $0.01 > p > 0.001$	0.00167	0.00333	0.01
c = $p < 0.001$	0.000167	0.000333	0.001

For the male rats only, exposures extended for four days into the 26th exposure month while the remaining male rats were being sacrificed. For mortality and tumor statistical analyses, all results obtained during this time period are included in the 25th exposure month.

Storage of Records

To the extent technically feasible and consistent with Good Laboratory Practices, Bushy Run Research Center will retain, safekeep and preserve all documents, data and material relevant to the research program in the BRRC Archives.

RESULTS AND DISCUSSION

Chamber Temperature and Relative Humidity

The chamber temperature and relative humidity differed only slightly from chamber to chamber and only slightly from one day to the next; however, there was more variation from winter to summer in these values as indicated in Tables 3 (temperature) and 4 (relative humidity). The overall mean temperature of the 5 chambers ranged from 70.0 to 71.2°F and the overall mean relative humidity from 49.8 to 51.4%.

Ethylene Oxide Vapor Concentration Determinations

The actual daily EO concentrations within the chambers were very close to the target concentrations and did not vary much from day to day. The overall mean of the measured chamber concentrations for the target concentrations of 100, 33, 10, 0 (Air Control I) and 0 ppm (Air Control II) were 101.1, 32.8, 9.9, 0.0 and 0.0 ppm, respectively. The monthly mean concentrations are presented in Table 5 and the daily mean concentrations in Appendix I, Tables A-4 and A-5.

Quality Control

The quality control procedures to monitor the general health status of the animals on the study were instituted prior to the commencement of exposures. The abnormalities encountered were within the usual limits for commercially available specific pathogen-free rats, and, therefore, the rats were determined to be of suitable quality for the long-term inhalation study.

The only significant event not related to the test treatment that affected the health status of the animals on the study was an outbreak of viral sialodacryoadenitis (SDA).

Sialodacryoadenitis Virus Infection

During the 15th exposure month, all rats on the study became infected with a virus. Clinical signs of infection noted during the 62nd and 63rd exposure week included conjunctivitis, proptosis, loss in body weight and enlarged salivary glands. These observations were recorded for all exposure groups, including the controls. The combination of these clinical signs, serologic analyses, gross observations, and pathognomonic histologic lesions in salivary, harderian and lacrimal glands confirmed the clinical diagnosis of sialodacryoadenitis virus infection. After the 64th exposure week, the exposures were temporarily terminated to permit recovery from the viral infection.

Prior to the infection, very low mortality had been observed from the beginning of the study. Of the initial 120 rats per sex per exposure group, no more than five in any group of one sex had died or were sacrificed because of a moribund condition. However, a total of 24 rats died during exposure weeks 64

Table 3

Chamber Temperature During the Exposure of Rats to Ethylene Oxide Vapor[1]

Exposure Month	Exposure Concentration 100 ppm Mean[2]	SD[3]	33 ppm Mean	SD	10 ppm Mean	SD	Control I 0 ppm Mean	SD	Control II 0 ppm Mean	SD
1	74.6	± 2.0	73.7	± 1.6	73.7	± 1.1	72.4	± 1.2	72.6	± 1.3
2	75.8	± 2.2	75.5	± 1.8	75.1	± 1.8	73.7	± 1.6	73.6	± 1.8
3	76.6	± 2.9	76.0	± 2.9	76.2	± 2.7	74.9	± 2.1	75.0	± 2.4
4	76.0	± 1.4	74.7	± 1.2	75.0	± 1.5	73.6	± 1.0	73.4	± 1.1
5	75.0	± 1.7	74.2	± 1.3	73.6	± 1.0	72.5	± 1.4	72.8	± 1.1
6	71.1	± 0.5	72.3	± 0.4	72.2	± 0.3	70.1	± 0.3	71.2	± 0.6
7	71.6	± 1.9	72.4	± 2.1	72.1	± 2.0	70.6	± 2.4	70.5	± 2.2
8	70.1	± 1.4	71.3	± 1.5	71.3	± 1.5	70.4	± 1.4	70.3	± 1.5
9	68.4	± 0.9	70.0	± 0.7	69.9	± 0.6	69.3	± 0.6	68.3	± 0.8
10	68.4	± 0.5	69.6	± 0.6	69.8	± 0.4	69.0	± 0.5	68.4	± 0.4
11	69.7	± 1.1	71.0	± 1.0	70.6	± 0.9	69.8	± 1.0	69.0	± 1.1
12	70.3	± 0.6	71.3	± 0.7	70.9	± 0.7	69.8	± 0.7	68.9	± 0.9
13	70.9	± 1.2	71.6	± 1.0	70.9	± 0.8	69.6	± 1.0	69.4	± 1.3
14	72.6	± 1.7	72.6	± 1.4	71.7	± 1.6	70.5	± 1.7	71.4	± 1.6
15*	73.2	± 1.4	72.9	± 1.4	71.8	± 1.3	70.2	± 1.4	71.1	± 1.2
16	74.5	± 1.2	73.9	± 1.2	72.2	± 1.1	72.2	± 1.2	72.9	± 1.0
17	72.5	± 2.2	72.4	± 2.1	70.9	± 2.1	70.8	± 2.1	71.6	± 1.9
18	69.6	± 1.1	69.8	± 1.3	68.8	± 1.3	68.4	± 1.2	69.2	± 1.3
19	68.7	± 0.8	68.9	± 0.8	68.3	± 0.7	67.7	± 0.9	68.4	± 0.7
20	68.5	± 0.9	69.0	± 0.9	68.9	± 0.9	68.8	± 0.9	68.7	± 0.9
21	67.8	± 0.8	69.0	± 0.8	67.8	± 0.7	68.6	± 0.8	68.2	± 1.2
22	67.4	± 0.9	68.9	± 0.9	68.1	± 0.7	68.9	± 1.2	68.4	± 1.6
23	67.7	± 0.9	68.2	± 1.2	67.6	± 0.9	67.6	± 0.9	67.6	± 1.1
24	68.1	± 1.4	68.6	± 1.1	67.5	± 1.0	68.0	± 1.0	67.6	± 1.0
25	68.0	± 1.9	68.0	± 1.6	66.8	± 1.4	66.9	± 1.6	68.1	± 2.0
26**	68.3	± 0.7	66.3	± 0.9	66.8	± 0.5	67.0	± 1.0	67.9	± 0.5
$\bar{X} \pm SD$[4]	71.0	± 3.0	71.2	± 2.5	70.7	± 2.6	70.0	± 2.1	70.2	± 2.2

[1]Approximately five temperature determinations were made during each exposure day. The first temperature reading, taken within 1-1/2 hours of the start of the exposure, was eliminated from this evaluation since this value was not representative of the equilibrated temperature values for the remaining time of the exposure. Any exposure which was less than three hours duration (total of 3 days) was also not included in this evaluation. A mean was calculated for each day and a mean of these means was calculated for each month.

[2]Units = Degrees Farenheit

[3]SD = Standard Deviation

[4]$\bar{X} \pm SD$ = Mean and standard deviation of monthly means

*Only two weeks of exposure because of SDA virus infection

**Only one week of exposure before all animals were sacrificed

Table 4

Chamber Percent Relative Humidity During the Exposure of Rats to Ethylene Oxide Vapor[1]

Exposure Month	Exposure Concentration 100 ppm Mean	100 ppm SD[2]	33 ppm Mean	33 ppm SD	10 ppm Mean	10 ppm SD	Control I 0 ppm Mean	Control I 0 ppm SD	Control II 0 ppm Mean	Control II 0 ppm SD
1	50.1	± 3.0	50.8	± 2.3	51.5	± 2.8	53.0	± 2.1	53.2	± 2.8
2	53.2	± 3.4	53.9	± 3.3	53.3	± 3.1	55.4	± 3.5	55.6	± 3.5
3	56.5	± 5.1	56.5	± 4.5	56.0	± 4.0	58.1	± 4.5	59.3	± 4.2
4	53.2	± 3.6	55.8	± 3.3	54.5	± 3.1	56.8	± 2.7	58.4	± 3.3
5	53.5	± 2.8	53.4	± 2.1	54.2	± 2.0	56.3	± 2.4	55.3	± 2.6
6	50.2	± 2.4	49.6	± 2.6	51.2	± 2.5	51.0	± 3.3	52.1	± 3.4
7	49.4	± 5.0	47.6	± 5.2	50.6	± 4.5	50.0	± 4.5	48.6	± 5.3
8	48.6	± 3.2	48.1	± 3.7	47.9	± 3.1	49.3	± 4.5	49.9	± 3.0
9	49.8	± 0.7	50.2	± 0.7	50.3	± 0.6	47.5	± 0.8	50.7	± 0.6
10	49.7	± 0.5	50.1	± 0.8	50.5	± 0.8	47.6	± 0.8	50.8	± 0.8
11	50.2	± 1.1	50.6	± 1.1	51.5	± 1.5	50.8	± 2.2	51.3	± 1.4
12	51.3	± 1.9	51.8	± 2.1	53.3	± 2.8	52.9	± 2.3	52.9	± 2.2
13	53.2	± 2.2	53.6	± 2.2	55.7	± 2.9	55.1	± 3.4	55.5	± 2.8
14	53.4	± 2.5	53.0	± 2.8	55.0	± 2.8	56.2	± 3.7	57.3	± 3.5
15*	52.1	± 2.6	52.9	± 2.0	55.0	± 3.1	57.0	± 3.3	56.9	± 2.8
16	50.4	± 1.1	51.8	± 1.2	53.0	± 1.3	55.3	± 1.9	52.5	± 1.4
17	48.7	± 2.5	50.3	± 2.4	50.9	± 2.9	52.8	± 2.8	51.4	± 2.6
18	45.0	± 2.0	47.2	± 1.9	46.8	± 2.3	48.3	± 2.3	47.0	± 2.1
19	46.3	± 1.8	47.6	± 1.9	47.0	± 2.6	46.6	± 2.5	45.8	± 2.2
20	43.3	± 2.9	44.4	± 3.1	42.6	± 4.1	42.9	± 3.6	42.5	± 3.4
21	42.0	± 1.4	43.6	± 1.0	43.2	± 1.6	44.6	± 1.4	40.9	± 1.4
22	41.1	± 3.2	43.5	± 1.7	42.5	± 1.5	43.6	± 1.4	42.8	± 1.9
23	44.8	± 2.3	44.7	± 2.5	44.3	± 2.9	45.6	± 2.1	45.1	± 2.1
24	48.0	± 3.0	48.1	± 3.5	48.5	± 3.8	48.7	± 3.3	48.5	± 3.5
25	53.8	± 4.4	53.5	± 4.4	53.8	± 4.5	53.4	± 5.0	54.8	± 4.6
26**	57.8	± 0.3	59.0	± 1.5	59.2	± 2.2	58.0	± 2.1	58.8	± 2.0
$\bar{X}$ ± SD[3]	49.8	± 4.2	50.4	± 4.0	50.8	± 4.4	51.4	± 4.6	51.4	± 5.2

[1]Approximately five humidity determinations were made during each exposure day. The first humidity reading, taken within 1 - 1-1/2 hours of the start of the exposure, was eliminated from this evaluation since this value was not representative of the equilibrated humidity values for the remaining time of the exposure. Any exposure which was less than three hours duration (total of 3 days) was also not included in this evaluation. A mean was calculated for each day and a mean of these means was calculated for each month.

[2]SD = Standard Deviation

[3]$\bar{X}$ ± SD = Mean and standard deviation of monthly means

*Only two weeks of exposure because of SDA virus infection

**Only one week of exposure before all animals were sacrificed

Table 5

Summary of Ethylene Oxide Exposure Monthly Concentration Determined by Gas Chromatography[1]

Exposure Month	Target Exposure Concentrations									
	100 ppm		33 ppm		10 ppm		0 ppm CI		0 ppm CII	
	$\bar{X}$	± SD	$\bar{X}$	± SD	$\bar{X}$	± SD	$\bar{X}$	± SD	$\bar{X}$	± SD
1	97.06	2.36	33.51	1.40	10.24	0.33	0.01	0.02	0.01	0.02
2	97.14	6.90	34.47	1.13	10.00	0.42	0.00	0.00	0.00	0.00
3	102.61	3.69	32.83	1.44	9.90	0.38	0.02	0.03	0.02	0.04
4	100.40	3.74	32.93	0.89	9.95	0.38	0.00	0.00	0.00	0.00
5	104.18	2.86	33.35	1.71	9.94	0.36	0.00	0.00	0.00	0.00
6	99.21	5.00	33.90	1.18	9.98	0.57	0.00	0.00	0.00	0.00
7	101.15	3.38	33.06	1.28	9.96	0.36	0.00	0.00	0.00	0.01
8	102.57	4.14	33.63	1.15	9.93	0.28	0.00	0.01	0.00	0.01
9	101.12	3.98	33.44	1.30	10.08	0.42	0.01	0.02	0.00	0.01
10	102.22	4.45	33.27	1.90	9.68	0.51	0.00	0.00	0.01	0.03
11	98.42	4.64	32.79	1.33	9.77	0.31	0.01	0.02	0.00	0.06
12	99.67	4.98	32.40	1.09	9.97	0.51	0.01	0.02	0.00	0.01
13	102.50	4.18	32.11	0.83	9.79	0.33	0.01	0.02	0.01	0.01
14	97.29	5.96	32.11	1.03	9.84	0.36	0.00	0.00	0.00	0.00
15	103.53	3.66	32.42	0.76	9.78	0.33	0.00	0.02	0.00	0.02
16	103.98	3.59	32.67	1.99	10.10	0.65	0.01	0.03	0.00	0.01
17	104.24	1.69	32.61	1.04	10.24	0.38	0.01	0.01	0.01	0.02
18	103.94	3.29	32.51	1.50	9.59	0.67	0.01	0.03	0.01	0.03
19	102.94	2.41	34.23	1.46	9.71	0.61	0.02	0.03	0.02	0.03
20	97.29	5.01	32.84	2.38	9.89	0.65	0.01	0.06	0.01	0.02
21	101.75	3.72	32.11	0.85	10.08	0.27	0.00	0.00	0.00	0.00
22	98.35	5.28	30.77	1.43	9.76	0.54	0.00	0.00	0.00	0.00
23	104.97	4.88	32.42	1.44	10.03	0.66	0.02	0.00	0.01	0.00
24	102.65	2.93	32.01	1.17	9.48	0.41	0.00	0.01	0.00	0.01
25	99.82	3.15	32.44	0.96	9.84	0.25	0.00	0.00	0.00	0.00

[1] The GC detection limit was 0.05 with occasionally a concentration printed that was less than this value.

and 65. There was a higher rate of mortality among female rats in the 100 ppm exposure group than in any other group. Gross and microscopic examination of tissues of the animals that died during this infection period revealed no pathologic findings sufficiently severe to explain the cause of death.

After two weeks of no exposures, most clinical signs associated with the infection subsided, the mortality rate decreased to the preinfection rate and the body weight returned to preinfection values, consequently exposures were restarted.

Observed long-term sequalae of this coronavirus disease, which is consistent with published information (Jacoby et al., 1975), included ophthalmologic lesions and chronic histologic changes in salivary gland tissues; both of which were present in EO-exposed as well as control rats. An increase in mortality has not been reported in the literature in association with this disease; however, most research on this disease has been with young, nonstressed rats.

Fate of the Animals

Presented in Appendix II, Tables A-6 and A-7, are listings of all animals on the study with the fate and the number of exposures before demise for all male and female rats, respectively.

The total number of male rats that died or were sacrificed in a moribund condition were 49, 39, 28, 31 and 29 for the males and 53, 31, 25, 19 and 20 for the females in the 100 ppm, 33 ppm, 10 ppm, Air Control I and Air Control II groups, respectively. One additional male in the 33 ppm group and one female in Air Control group I were accidentally killed.

Tables 6 and 7 contain the cumulative mortality data and statistical significances of male and female rats, respectively, that died or were sacrificed in a moribund condition for each exposure month. The mortality data are graphically presented for males and females in Figures 2A and 2B, respectively. The cumulative percentage dying in the 100 ppm group for both sexes was significantly different from that of one or both controls for at least the last four exposure months of the study. Some significant differences were observed in the 33 ppm group for the males.

It is noted that during the 15th exposure month, mortality increased in both EO-exposed and control groups. This event was related to the sialodacryoadenitis (SDA) virus infection, previously described. More animals died in the 100 and 33 ppm groups than in the others and mortality was elevated earlier and to a greater extent in the females than in the males. The incidence of mortality decreased during the month after the infection to approximately the level prior to the infection. Since this virus outbreak contributed significantly to mortality for the 100 and 33 ppm groups, the mortality data were re-evaluated using the number of rats alive at the beginning of month 17, following the SDA virus infection, as the starting point.

Table 6

Cumulative Percentages[1] of Male Rats Dying or Sacrificed in a Moribund Condition After Exposure to Ethylene Oxide Vapor

Exposure Month	Exposure Concentration					
	100 ppm	33 ppm	10 ppm	Air Control I	Air Control II	Combined Controls
1	0.0	0.0	0.0	0.0	0.0	0.0
2	0.0	0.0	0.0	0.0	0.0	0.0
3	0.0	0.0	0.0	0.0	0.0	0.0
4	0.0	0.0	0.0	0.0	0.0	0.0
5	0.0	0.0	0.0	0.8	0.0	0.4
6	0.0	0.0	0.0	0.8	0.0	0.4
7	0.0	0.0	0.0	0.8	0.0	0.4
8	0.0	0.0	0.0	0.8	0.0	0.4
9	0.0	0.9	0.9	0.8	0.0	0.4
10	0.0	1.8	0.9	0.8	0.0	0.4
11	0.0	2.8	0.9	0.8	0.0	0.4
12	1.0	2.8	0.9	0.8	0.0	0.4
13	1.0	4.8	0.9	0.8	0.0	0.4
14	3.0	4.8	0.9	1.8	0.0	0.9
15	7.0	6.8	0.9	1.8	2.0	1.9
16	7.0	8.8	1.9	1.8	2.0	1.9
17	7.0	9.8	2.9	2.9	4.1	3.5
18	10.4	9.8	2.9	5.1	5.2	5.2
19	11.7	12.5	2.9	5.1	5.2	5.2
20	18.2	15.1	8.0	9.0	6.5	7.8
21	$24.7^{(-,-,a)}$	20.3	10.6	11.5	10.4	11.0
22	$27.3^{(-,-,-)}$	$29.4^{(-,a,a)}$	14.4	17.9	11.7	14.8
23	$44.2^{(a,c,c)}$	$36.0^{(-,b,b)}$	18.3	21.8	13.0	17.4
24	$50.7^{(a,c,c)}$	$39.9^{(-,a,-)}$	25.9	29.5	20.8	25.2
24.5	$55.9^{(a,b,c)}$	42.5	31.0	34.6	28.6	31.6
25.0	$65.2^{(a,-,b)}$	54.2	38.3	41.9	42.6	42.3

a = $0.05 > p > 0.01$ b = $0.01 > p > 0.001$ c = $p < 0.001$

First letter of superscript denotes degree of significance vs. Control I group; second letter denotes degree of significance vs. Control II group; third letter denotes degree of significance vs. Combined Controls (C-I plus C-II). Bracketed superscripts denote values significantly higher than those of control groups.

[1]Life Table Analysis

Table 7

Cumulative Percentages[1] of Female Rats Dying or Sacrificed in a Moribund Condition After Exposure to Ethylene Oxide Vapor

Exposure Month	Exposure Concentration 100 ppm	33 ppm	10 ppm	Air Control I	Air Control II	Combined Controls
1	0.0	0.0	0.0	0.8	0.0	0.4
2	0.0	0.0	0.0	0.8	0.0	0.4
3	0.0	0.0	0.0	0.8	0.0	0.4
4	0.0	0.8	0.0	0.8	0.0	0.4
5	0.0	0.8	0.0	0.8	0.0	0.4
6	0.0	0.8	0.0	0.8	0.0	0.4
7	0.0	0.8	0.0	0.8	0.0	0.4
8	0.0	0.8	0.0	0.8	0.0	0.4
9	0.0	0.8	0.0	0.8	0.0	0.4
10	1.8	0.8	0.0	0.8	0.0	0.4
11	1.8	0.8	0.0	0.8	0.0	0.4
12	1.8	0.8	0.0	0.8	0.0	0.4
13	2.8	1.8	0.0	0.8	0.0	0.4
14	3.9	1.8	0.0	0.8	0.0	0.4
15	$16.0^{(b,b,b)}$	5.9	2.0	2.8	3.1	3.0
16	$18.0^{(b,b,b)}$	5.9	3.0	3.8	3.1	3.5
17	$21.1^{(c,c,c)}$	6.9	5.0	3.8	3.1	3.5
18	$22.2^{(b,c,c)}$	10.3	6.2	6.1	4.3	5.2
19	$25.0^{(a,c,c)}$	15.5	11.3	8.6	5.6	7.1
20	$30.4^{(b,a,b)}$	16.8	11.3	9.9	12.3	11.0
21	$34.5^{(c,a,c)}$	22.0	12.6	9.9	16.3	13.0
22	$41.3^{(c,b,c)}$	24.6	13.9	9.9	18.9	14.3
23	$49.5^{(c,b,c)}$	32.4	24.2	18.8	22.9	20.8
24	$63.3^{(c,c,c)}$	35.2	28.5	22.9	25.8	24.3
24.5	$70.0^{(c,c,c)}$	41.1	34.7	25.9	25.8	25.9

a = $0.05 > p > 0.01$ b = $0.01 > p > 0.001$ c = $p < 0.001$

First letter of superscript denotes degree of significance vs. Control I group; second letter denotes degree of significance vs. Control II group; third letter denotes degree of significance vs. Combined Controls (C-I plus C-II). Bracketed superscripts denote values significantly higher than those of control groups.

[1]Life Table Analysis

WPC/1063

Figure 2A

CUMULATIVE PERCENTAGES OF RATS DYING OR SACRIFICED IN A MORIBUND CONDITION AFTER EXPOSURE TO ETHYLENE OXIDE VAPOR.

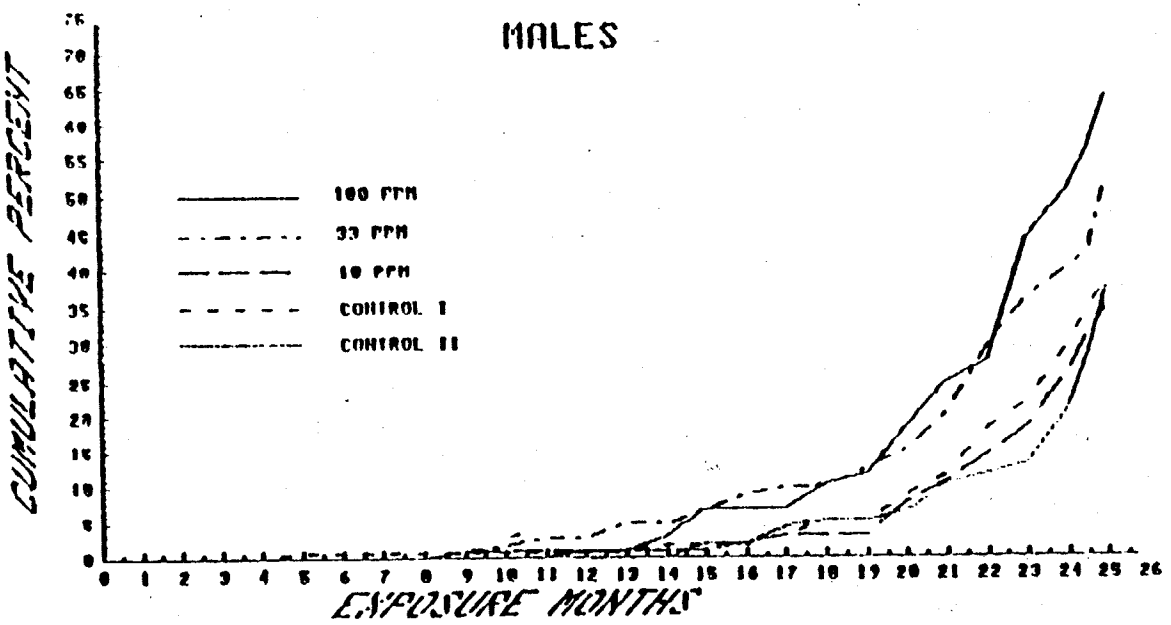


Figure 2B

CUMULATIVE PERCENTAGES OF RATS DYING OR SACRIFICED IN A MORIBUND CONDITION AFTER EXPOSURE TO ETHYLENE OXIDE VAPOR.

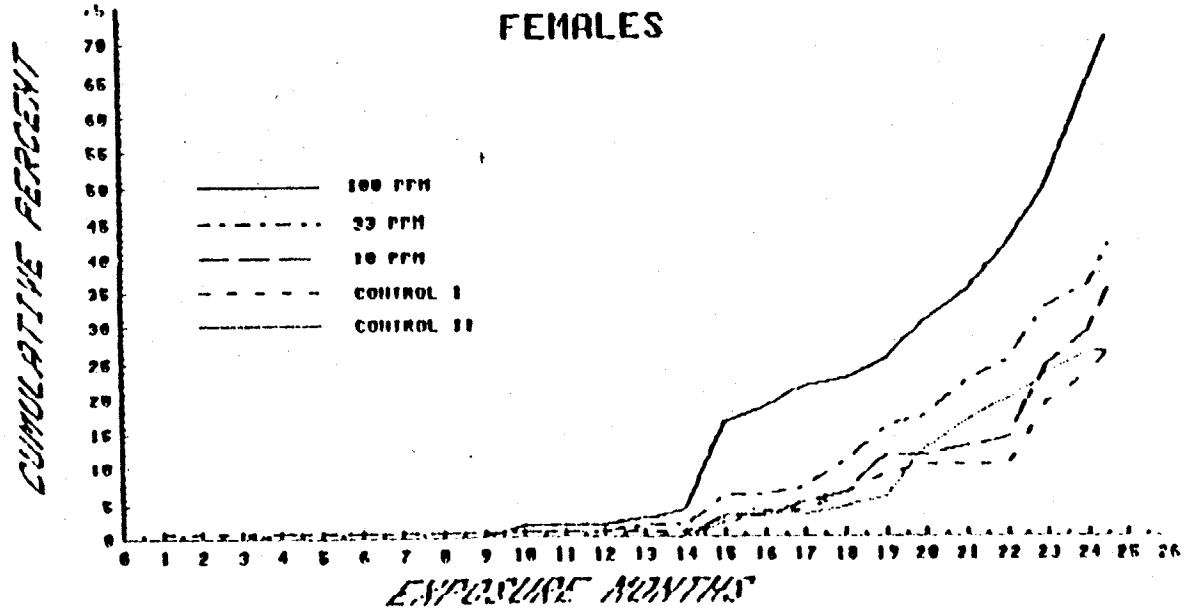


Figure 2

The results of these calculations are presented in Tables 8 and 9 and Figure 3A and 3B for males and females, respectively. This recalculation could allow for mortality rate to be determined without the initial interfering effect of the SDA virus infection included.

For both sexes of all groups, the rate of mortality increased at approximately the 20th exposure month. This is not unusual for the normal aging Fischer 344 rat. It was not until the 22nd or 23rd exposure month that significantly higher mortality values (cumulative percentage) were noted for both sexes of the 100 ppm group. At no time interval was the cumulative percentage mortality value for either sex in the 33 ppm group significantly different from that of both controls. However, from the 21st month on, the values for both sexes of the 33 ppm group were numerically greater than those of both control groups. At no time were there significant increases in mortality present in the 10 ppm exposure group of either sex.

Animal Observations

The type of observations made daily for one group was basically similar to those made for the rest of the groups. No treatment-related observations were made other than an increase in death and morbidity in the EO-exposed animals, which is discussed above.

The only statistically significantly increased values of the 100 ppm group, noted in the monthly in-depth observations, were in the frequency of fur discoloration around the dorsal neck region and the number of failures for the hind limb lift reflex test. These occurred only once for each, early in the study, and are of no toxicologic significance; the hind limb reflex result is believed to have occurred because of fatigue of the male rats following a preceding test which was run for this observation period only. A summary of the monthly in-depth clinical observations is presented in Tables 10 and 11 for male and female rats, respectively.

Body Weight Determinations

The day before the first exposure, the group means for male rats and female rats were very close in value and the variances were equivalent as indicated in Tables 12 for males and 13 for females. The change in body weight from this reference point was calculated at each weighing interval and is also presented in these Tables. These data are graphically presented in Figures 4 and 5 for male and female rats, respectively.

A statistically significant depression in body weight gain was obtained at the end of the third exposure week (13 exposures completed) in the females and at the end of the fifth exposure week (23 exposures completed) in the males of the 100 ppm group. Thoughout the rest of the two-year study this treatment-related effect was observed.

At no time during the study were the changes in body weight of the 33 ppm group of male rats significantly lower in value when compared to the controls. However, statistically significantly lower mean values for the 33 ppm females,

Table 8

Cumulative Percentages[1] of Male Rats Alive
at the Beginning of Month 17, But Dying or Sacrificed
in a Moribund Condition After Subsequent Exposure to Ethylene Oxide Vapor

Exposure Month	Exposure Concentration 100 ppm	33 ppm	10 ppm	Air Control I	Air Control II	Combined Controls
17	0.0	1.1	1.0	1.0	2.1	1.6
18	3.7	1.1	1.0	3.3	3.2	3.3
19	5.0	4.0	1.0	3.3	3.2	3.3
20	12.0	6.8	6.2	7.2	4.6	5.9
21	19.0	12.6	8.8	9.9	8.6	9.2
22	21.8	22.6	12.8	16.4	9.9	13.2
23	$40.0^{(a,c,c)}$	$29.8^{(-,a,-)}$	16.7	20.3	11.2	15.8
24	$46.9^{(-,c,b)}$	34.1	24.5	28.2	19.2	23.7
24.5	$52.5^{(-,b,b)}$	36.9	29.7	33.4	27.1	30.3
25.0	$62.5^{(-,-,a)}$	49.8	37.1	40.8	41.4	41.2

a = $0.05 > p > 0.01$ b = $0.01 > p > 0.001$ c = $p < 0.001$

First letter of superscript denotes degree of significance vs. Control I group; second letter denotes degree of significance vs. Control II group; third letter denotes degree of significance vs. Combined Controls (C-I plus C-II). Bracketed superscripts denote values significantly higher than those of control groups.

[1]Life Table Analysis

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Table 9

Cumulative Percentages[1] of Female Rats Alive
at the Beginning of Month 17, But Dying or Sacrificed
in a Moribund Condition After Subsequent Exposure to Ethylene Oxide Vapor

Exposure Month	Exposure Concentration					
	100 ppm	33 ppm	10 ppm	Air Control I	Air Control II	Combined Controls
17	3.7	1.1	2.1	0.0	0.0	0.0
18	5.1	4.7	3.2	2.3	1.2	1.8
19	8.4	10.2	8.6	5.0	2.6	3.8
20	15.1	11.6	8.6	6.3	9.4	7.8
21	20.1	17.1	9.9	6.3	13.6	9.8
22	$28.4^{(b,-,a)}$	19.9	11.2	$6.3^{-,a}$	$16.3^{(a,-)}$	11.2
23	$38.4^{(a,-,b)}$	28.2	21.8	15.5	20.4	17.9
24	$55.2^{(c,c,c)}$	31.2	26.2	19.8	23.4	21.6
24.5	$63.4^{(c,c,c)}$	37.4	32.6	22.9	23.4	23.2

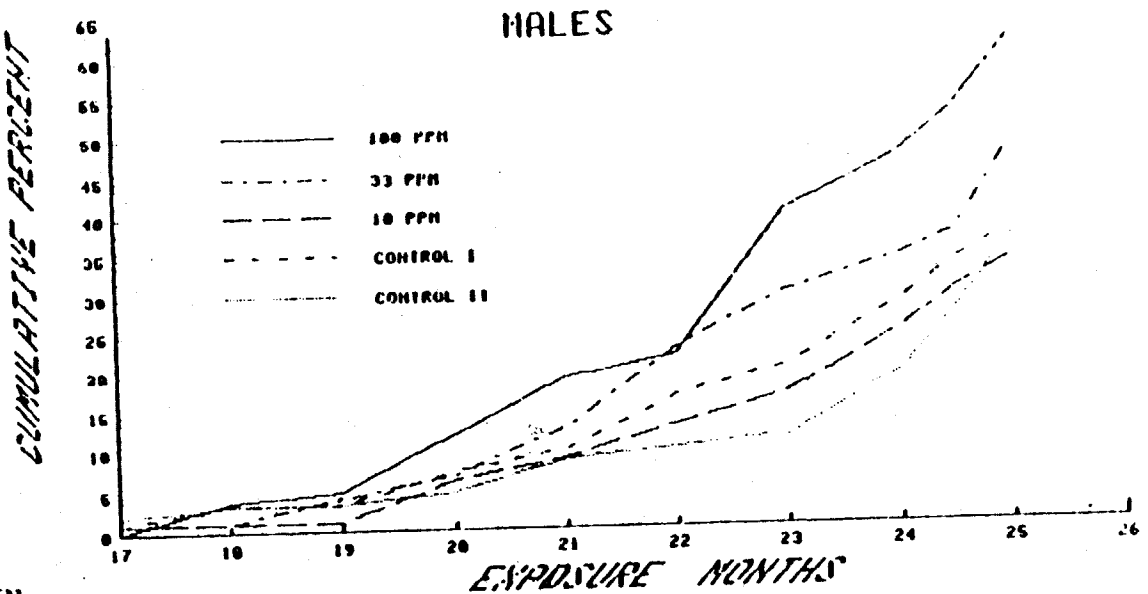
a = $0.05 > p > 0.01$ b = $0.01 > p > 0.001$ c = $p < 0.001$

First letter of superscript denotes degree of significance vs. Control I group; second letter denotes degree of significance vs. Control II group; third letter denotes degree of significance vs. Combined Controls (C-I plus C-II). Bracketed superscripts denote values significantly higher than those of control groups.

[1]Life Table Analysis

WPC/1063

Figure 3A



CUMULATIVE PERCENTAGES OF RATS DYING OR SACRIFICED IN A MORIBUND CONDITION AFTER EXPOSURE TO ETHYLENE OXIDE VAPOR.

Figure 3B

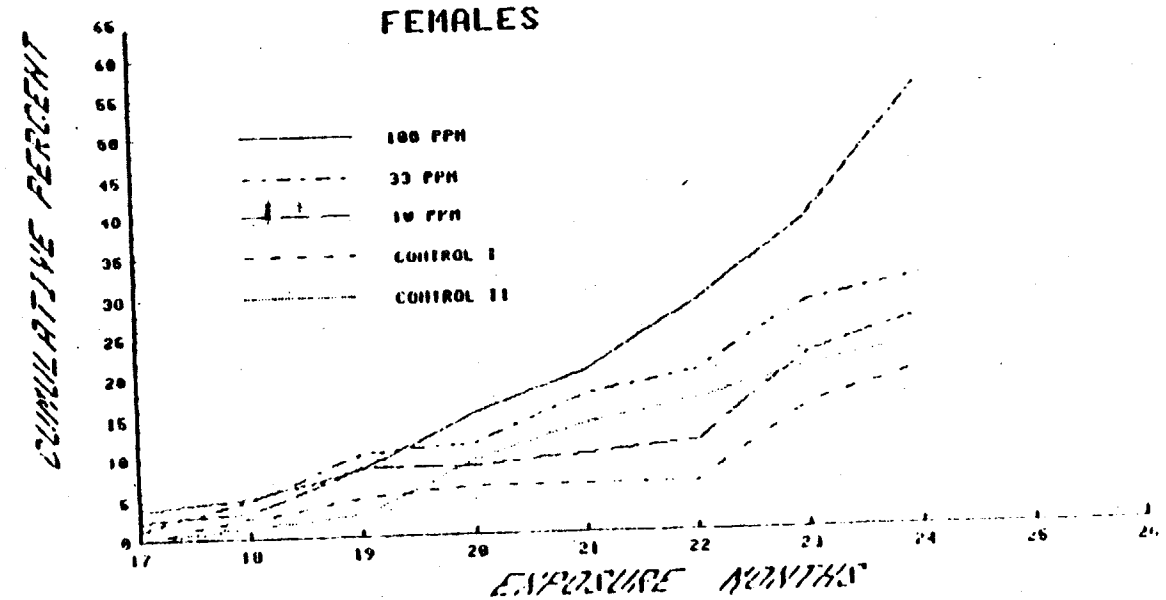


Table 10

Summary of Observations Recorded at Monthly Intervals on a Select Group of Male Rats During the Two-Year Ethylene Oxide Inhalation Vapor Study

Observations	Exposure Levels, ppm	Percentage[1] of Rats with Observation During Exposure Week																							
		4	8	12	16	20	24	28	32	35	41	44	48	52	56	60	64	68	72	76	81	85	89	94	97	101
Fur, reddish brown "cape"	100	45	65	100[a]	100	95	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
	0	55	40	70	95	90	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Red-brown material around nares	100	15	70	65	60	55	75	55	55	45	40	50	40	30	50	20	24	18	12	12	19	25	33	31	27	30
	0	40	55	80	60	80	75	55	70	75	50	60	50	45	55	42	22	11	28	28	12	31	12	27	29	16
Conjunctivitis	100	0	5	5	5	0	0	0	0	0	0	5	10	10	5	10	18	18	24	24	19	31	47	42	55	50
	0	0	5	0	5	5	0	0	5	5	5	15	10	10	10	11	11	17	11	11	12	12	12	20	14	29
Soft stool	100	2/13	1/8	2/11	0/8	0/8	0/12	0/12	0/8	2/6	1/4	0/4	0/4	1/4	0/2	1/6	0/3	1/4	0/6	0/7	0/2	0/2	0/1	0/3	0/5	0/1
	0	0/8	0/10	1/10	0/10	0/11	0/11	1/7	0/10	1/13	0/6	1/9	1/7	1/10	0/5	1/5	0/2	1/7	0/7	0/6	0/4	0/4	1/6	0/5	0/6	0/6
Hind-limb lift reflex test; failed only once	100	-	65[b]	5	5	0	0	5	0	0	0	5	0	0	0	0	0	0	0	0	0	19	8	10	0	12
	0	-	20	5	5	10	5	0	0	0	0	0	0	0	5	0	0	0	0	0	0	0	0	7	0	14
-failed once or twice[2]	100	-	35[a]	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	19	0	0	0	0
	0	-	5	5	0	5	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	7
-failed more than twice[2]	100	-	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	0	0	0	0
	0	-	0	5	0	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	7
Emaciation	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0	13	8	9	20
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	7
Salivation	100	50	0	5	10	20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	20	0	0	0	15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hypoactivity	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	17	0	14
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	14

a = $0.05 > p > 0.01$ b = $0.01 > p > 0.001$

[1]Percentages are expressed for all observations with the exception of ratios for "soft-stool". N = 20 from 100 ppm group and 20 from the control group (10 from each control group) per observation period 4 through 56 (except 19 rats of 100 ppm group for hind limb lift reflex test at week 20); 10 [illegible] thereafter for 100 ppm ethylene oxide and 14 to 19 for controls. No noteworthy observations were recorded for pilo-erection, lacrimation, abnormal respiration, kyphosis, ataxia, abnormal muscle contraction, righting reflex or irritable behavior.

[2]The rats that passed the hind-limb lift reflex test during the first trial were not retested for the second trial; similarly those that passed the second trial were not retested in the third trial.

Table 11

Summary of Observations Recorded at Monthly Intervals on a Select Group of Female Rats During the Two-Year Ethylene Oxide Inhalation Vapor Study

Observation	Exposure levels, ppm	Percentage[1] of Rats with Observation During Exposure Week																								
		4	8	12	16	20	24	28	32	35	41	44	48	52	56	60	64	68	72	76	81	85	89	94	97	101
Fur, reddish brown "caps"	100	40	100	95	95	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	94	100	100	100
	0	60	95	80	95	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	94	94
Red-brown material around nares	100	35	70	70	65	55	70	75	75	60	55	80	40	30	45	45	30	28	24[b]	41	24	31	19	38	50	40
	0	40	50	80	75	65	70	65	70	70	65	70	50	40	60	35	50	47	74	47	28	24	29	35	41	47
Conjunctivitis	100	0	0	0	0	10	10	10	10	10	15	15	20	10	10	10	50	44	41	41	35	25	31	31	29	20
	0	0	0	0	5	20	15	5	10	5	10	25	10	15	10	15	25	36	42	32	28	35	35	35	35	35
Soft stool	100	3/14	0/8	1/7	0/9	0/14	0/12	0/13	0/13	1/7	1/8	0/6	0/3	0/2	0/3	0/3	0/3	0/5	0/8	0/6	0/3	0/4	1/5	0/12	0/5	0/2
	0	2/15	0/7	0/7	0/6	0/11	2/11	0/11	0/15	0/10	0/5	0/5	0/2	0/4	0/1	0/3	0/0	0/2	0/8	1/10	0/2	0/2	0/4	0/6	1/8	0/6
Hind-limb lift reflex test; failed only once	100	0	5	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	7	14	0	0
	0	10	5	0	0	0	0	0	0	0	5	0	0	0	5	0	0	0	0	0	0	0	0	0	6	0
-failed once or twice[2]	100	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	7	7	0	0
	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0
-failed more than twice[2]	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	7	7	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0
Inactivation	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0	6	6
Salivation	100	40	0	0	15	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	20	0	0	5	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hypoactivity	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	12	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0

[b] = $0.01 > p > 0.001$

[1] Percentages are expressed for all observations with the exception of ratios for "soft-stool". N = 20 from 100 ppm group and 20 from the control groups (10 from each control group) per observation period 4 through 64; 10 to 18 thereafter for 100 ppm ethylene oxide and 17 to 19 for controls. No noteworthy observations were recorded for pilo-erection, lacrimation, abnormal respiration, kyphosis, ataxia, abnormal muscle contraction, righting reflex or irritable behavior.

[2] The rats that missed the hind-limb lift reflex test during the first trial were not retested for the second trial; similarly those that passed the second trial were not retested in the third trial.

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Table 12

Body Weight Changes of Male Fischer 344 Rats Exposed to Ethylene Oxide

Exposure Week	N (Range)	Exposure Group: 100 ppm Mean	±	SD	33 ppm Mean	±	SD	10 ppm Mean	±	SD	0 ppm CII Mean	±	SD	0 ppm CII Mean	±	SD
		Body weight, grams, on day 0														
0		118.0		14.8	114.4		14.0	118.4		14.9	118.9		14.8	115.9		13.4
		Body weight change, grams, from weight on day 0														
1	120	18.5		2.7	18.8		2.4	18.2[a,-]		2.9	19.0		2.8	18.8		4.6
2	120	51.0		6.4	50.8		6.0	50.4		5.5	51.5		5.9	49.8		7.7
3	120	75.4		9.1	76.6		9.6	76.2		8.3	77.2		8.7	75.4		10.9
4	120	93.2		11.3	95.4		12.7	95.9		10.2	96.1		12.7	95.4		13.1
5	120	106.8[c,a]		13.9	110.8		14.9	111.7		12.0	111.8		14.8	111.2		15.8
6	120	120.3[b,-]		15.0	124.2		16.2	125.5		13.9	126.0		16.6	124.3		17.3
7	120	130.2[b,b]		16.0	136.3		16.9	136.9		14.6	137.0		17.0	135.9		17.4
8	120	143.0[b,b]		16.7	150.3		18.0	151.1		15.9	150.6		18.1	149.0		18.7
9	120	153.5[b,a]		17.6	160.1		18.8	159.3		16.8	161.1		18.8	158.3		19.8
10	120	158.4[c,b]		18.5	165.2		18.9	165.4		16.8	167.9		19.7	165.4		20.2
11	119	160.1[c,b]		18.8	169.0		20.2	167.3		17.0	171.3		20.0	167.4		20.3
12	118-119	174.7[b,a]		20.1	181.9		19.9	182.0		19.1	183.1		21.1	180.5		20.9
15	119	192.3[c,a]		20.4	202.8		21.5	201.5		18.9	204.8[(-,a)]		23.2	198.9[a,-]		22.7
17	119	197.8[c,a]		21.0	208.7		21.9	207.0		19.6	209.3		23.3	204.9		22.8
19	119	210.4[b,-]		21.9	221.3[(-,a)]		21.9	220.2[(-,a)]		20.5	221.7[(-,a)]		24.2	217.2[a,-]		23.8
20	119	214.6[c,b]		21.6	228.2		22.4	226.6		21.5	228.1		25.2	223.4		24.6
22	118-119	219.9[c,c]		22.1	235.2		23.3	232.6		22.0	236.5		26.0	232.6		25.7
24	118-119	226.1[c,c]		24.0	242.1		24.4	239.1*		22.9	241.6		26.8	238.3		25.2
26	118-119	237.3[c,c]		23.6	253.3		25.6	249.4		25.5	255.7		27.4	249.6		28.7
28	108-109	243.0[c,c]		25.2	258.5		25.5	254.1[a,-]		26.5	261.7		27.9	254.0		32.4
30	108-109	249.0[c,c]		25.6	266.9		25.9	262.8		25.8	270.5		29.7	263.6		29.9
34	108-109	254.9[c,c]		25.4	274.3		27.0	272.1		27.1	277.2		29.5	271.3		28.9
38	108-109	262.8[c,c]		25.8	287.9[(-,c)]		28.1	281.3[-,c]		33.4	288.8[(-,c)]		29.8	281.3[c,-]		30.5
42	108-109	272.3[c,c]		27.9	294.2		29.4	292.9		28.0	298.1[(-,a)]		31.5	288.1[a,-]		30.2
46	106-109	276.9[c,c]		27.5	300.2		28.8	296.3		30.5	302.8[(-,a)]		31.8	292.1[a,-]		32.1
50	106-109	280.6[c,c]		29.5	305.7		29.5	301.8		31.2	305.2		30.7	299.4		32.3
54	96-99	283.1[c,c]		29.0	308.8		32.1	305.5		30.9	310.7		31.5	306.0		32.0
58	94-99	291.2[c,c]		29.4	316.4		29.3	310.6		32.3	316.1		32.5	310.3		33.0
63	93-98	298.6[c,c]		29.6	294.7		31.2	287.7		33.4	296.8		33.9	288.4		36.3
65	92-98	272.5[c,c]		30.6	307.9		29.9	300.2		33.6	310.0		32.7	300.6		35.9
66	92-98	282.2[c,c]		31.7	314.9		30.0	306.9		33.8	316.7		32.5	308.7		35.8
67	92-98	291.6[c,c]		30.7	316.0		53.8	315.0		35.0	321.9		32.9	312.3		36.9
71	91-97	297.0[c,c]		29.8	324.1		57.1	317.6		34.5	326.9		32.6	322.9		33.5
75	89-96	298.4[c,c]		30.3	330.6		33.3	320.2[a,-]		34.4	330.9		33.7	325.9		33.3
79	69-76	300.7[c,c]		29.3	329.6		35.2	320.0		40.9	330.8		34.7	330.0		36.1
83	68-77	296.6[c,c]		29.3	327.7		36.4	311.0[b,-]		42.3	328.8		39.4	323.2		38.1
87**	64-73	287.8		35.2	323.2		40.5	314.7		36.5	326.8		43.6	320.9		36.9
91	60-71	288.7[c,c]		32.0	324.8		38.8	311.5[a,-]		34.3	328.7		49.6	317.1		40.4
95	56-68	278.4[c,c]		38.3	323.8		48.9	311.2		37.7	318.6		45.4	313.3		42.4
99	48-68	275.2[c,b]		44.0	311.2		35.8	307.5		36.4	307.9		48.2	300.6		46.7
103	40-67	267.1[c,a]		37.2	298.4		36.7	289.2		52.9	295.1		39.4	286.5		51.3

a = $0.05 > p > 0.01$ b = $0.01 > p > 0.001$ c = $p < 0.001$

First letter of superscript denotes degree of significance vs. Control I group; second letter denotes degree of significance vs. Control II group. Bracketed superscripts denote values significantly higher than those of control groups.

SD = Standard Deviation

*60 rats not included in statistics because without feed prior to weighing; N = 59

**No statistical analysis for data of this exposure week.

DHC/11295A-7

Table 13

Body Weight Changes of Female Fischer 344 Rats Exposed to Ethylene Oxide

Exposure Week	N (Range)	Exposure Group: 100 ppm Mean	±	SD	33 ppm Mean	±	SD	10 ppm Mean	±	SD	0 ppm CI Mean	±	SD	0 ppm CII Mean	±	SD
		Body weight, grams, on day 0														
0		98.0		9.3	96.1		9.9	95.5		8.8	97.5		9.1	95.2		8.7
		Body weight change, grams, from weight on day 0														
1	120	10.3(a,-)		1.9	10.4(b,-)		2.1	10.7(b,-)		2.3	9.6-,b		2.8	10.5(b,-)		2.0
2	120	24.0		5.1	23.9		4.4	25.9(b,-)		4.5	24.1		5.0	24.7		4.3
3	120	32.9b,b		6.6	34.4		5.9	36.9		6.3	35.4		6.7	35.8		6.0
4	120	40.0c,c		8.0	42.1		7.6	45.7(b,a)		6.9	43.2		7.3	43.6		6.7
5	120	46.1c,c		8.9	50.2		8.3	53.5(a,a)		7.7	51.4		8.3	51.0		7.5
6	119-120	52.7c,c		9.8	55.6		9.2	60.6(a,a)		8.9	57.9		10.4	57.9		8.7
7	119-120	56.6c,c		10.2	61.1		9.6	66.2(a,b)		9.4	63.3		9.9	62.3		9.5
8	119-120	60.7c,c		10.4	65.6		10.0	70.8(a,b)		9.8	67.6		10.4	67.1		9.7
9	119-120	65.5c,c		10.8	69.1a,-		9.9	74.1		10.1	72.3		10.4	71.4		9.7
10	119-120	68.2c,c		11.0	72.5c,a		10.4	78.0		10.7	77.4		11.3	76.0		10.0
11	119	71.1c,c		11.7	73.8c,b		10.5	79.3		10.5	81.6(-,a)		11.7	78.3a,-		10.1
13	119	74.5c,c		12.2	79.7b,b		11.1	86.7		11.2	84.8		11.8	84.2		11.3
15	119	80.6c,c		11.8	87.3c,-		10.8	93.4(-,a)		11.0	92.4		11.8	90.2		10.8
17	118-119	83.4c,c		11.6	89.5c,a		11.6	96.9(-,a)		10.8	95.4		11.8	93.0		11.0
19	118-119	86.4c,c		11.7	92.3c,c		11.3	100.1		10.8	99.0		11.8	97.9		11.2
20	118-119	88.2c,c		11.8	95.2c,c		11.2	103.0		11.5	101.4		12.5	100.8		11.1
22	118-119	89.5c,c		12.2	97.1c,b		12.2	104.7		11.0	103.0		12.7	102.0		11.8
24	118-119	93.0c,c		12.9	100.8c,c		12.0	104.5a		10.8	106.8		12.8	106.4		12.7
26	118-119	97.2c,c		12.8	105.6c,a		11.5	112.8		11.9	112.8		13.1	109.7		12.9
28	108-109	97.1c,c		12.8	105.1c,a		12.6	111.0		11.6	112.0		14.3	108.7		12.8
30	108-109	98.3c,c		13.8	106.6c,b		12.6	114.3		12.2	115.3		17.4	111.5		12.6
34	108-109	99.7c,c		15.9	110.2c,c		12.2	118.5		11.1	118.1		12.9	115.9		12.1
38	108-109	104.9c,c		13.3	115.7c,c		12.3	123.5		12.2	122.0		14.0	122.3		13.0
42	107-109	113.2c,c		23.9	117.3c,c		13.4	127.6		11.3	125.2		15.1	125.5		14.2
46	107-109	108.7c,c		16.4	118.1c,c		13.8	128.9		13.6	127.4		16.4	126.2		15.3
50	107-109	115.9c,c		16.9	125.6c,c		13.6	136.6		14.3	133.2		16.9	133.6		15.9
54	97-99	118.6c,c		19.0	131.8a,c		13.6	142.4		14.8	137.8		18.8	139.4		16.8
58	96-99	121.9c,c		18.8	136.6a,b		15.2	146.0		14.9	142.8		19.1	142.8		17.1
63	94-99	118.0c,c		18.3	130.5a,b		15.5	139.9		14.6	135.6		18.8	137.8		16.3
65	84-98	122.4c,c		16.8	136.3-,a		16.3	144.6		15.2	140.3		19.9	141.9		17.7
66	84-97	126.4c,c		18.4	140.1		15.7	149.0(a,-)		15.9	143.6		20.2	144.7		17.0
67	83-97	131.6c,c		19.2	144.9-,a		16.4	153.1(a,-)		16.3	146.3		20.5	151.2		17.3
71	81-96	142.2c,c		19.0	155.5-,b		17.3	164.6(a,-)		16.9	159.1		19.6	162.7		17.9
75	78-96	144.0c,c		19.3	160.5a,a		19.2	171.5		16.4	166.0		19.4	166.2		18.4
79	58-74	149.0c,c		20.7	167.3		25.6	174.1		16.4	170.2		18.5	171.3		15.7
83	55-72	145.6c,c		20.9	164.1a,-		21.7	175.4(-,a)		13.8	171.1		19.2	169.2		17.4
87	51-71	148.6c,c		24.8	168.3		27.5	177.3		13.8	173.3		20.1	172.3		19.8
91	50-71	151.0c,c		22.8	176.3		34.5	184.4(a,-)		19.0	176.8		20.6	180.0		22.9
95	46-71	150.8c,c		28.3	183.0		42.8	184.2		22.2	177.5		27.0	184.2		23.3
99	40-69	150.8b,c		31.0	182.9		45.2	178.9		40.7	172.4a,-		36.6	184.2(a,-)		29.7
103	34-62	153.1b,c		41.2	170.4		28.1	175.9		28.8	173.4		31.8	179.7		35.1

a = $0.05 > p > 0.01$ b = $0.01 > p > 0.001$ c = $p < 0.001$

First letter of superscript denotes degree of significance vs. Control I group; second letter denotes degree of significance vs. Control II group. Bracketed superscripts denote values significantly higher than those of control groups.

SD = Standard Deviation

*60 rats not included in statistics because without feed prior to weighing; N = 59

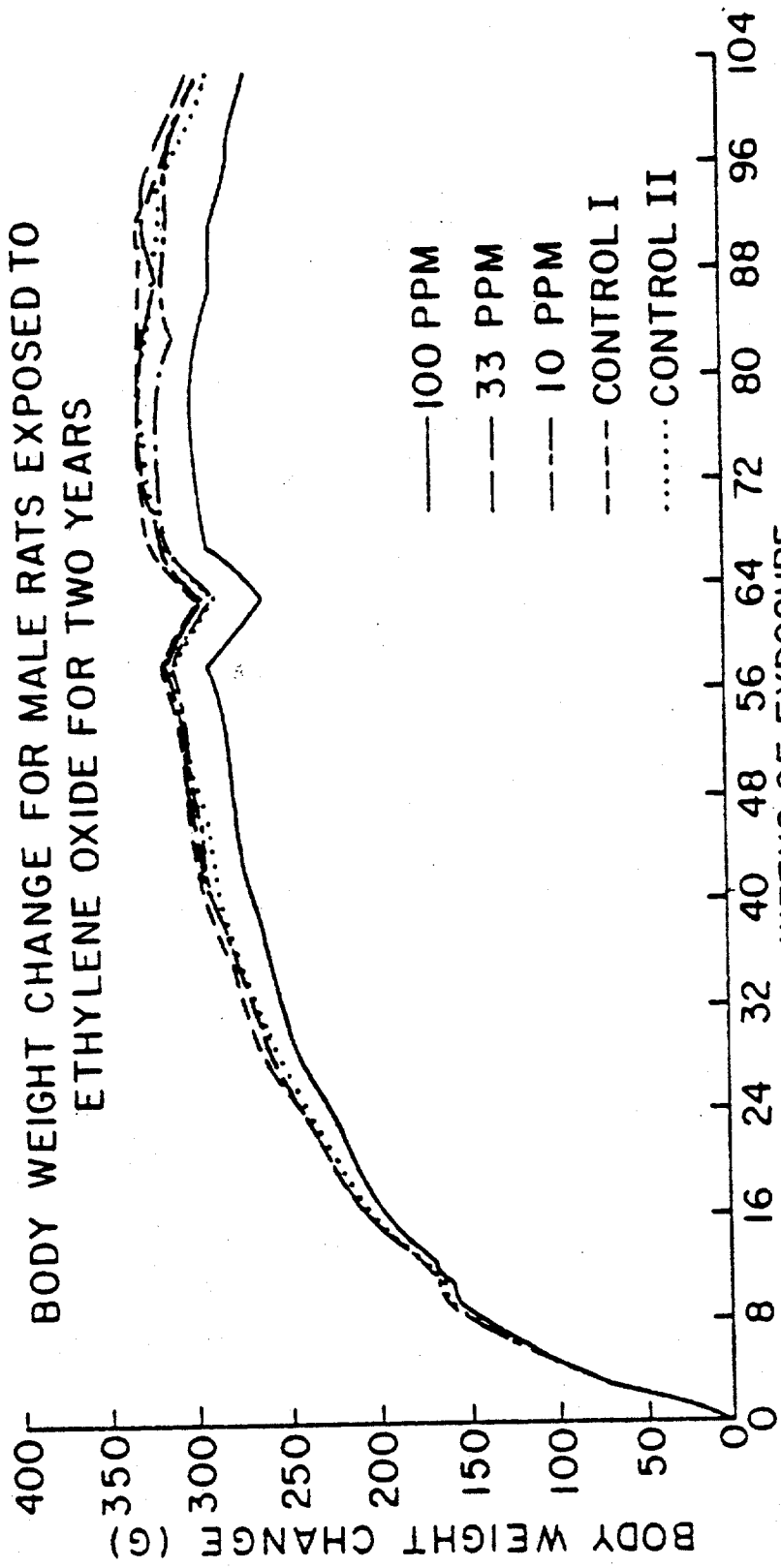
BODY WEIGHT CHANGE FOR MALE RATS EXPOSED TO ETHYLENE OXIDE FOR TWO YEARS
BODY WEIGHT CHANGE (G)
400
350
300
250
200
150
100
50
0
0
8
16
24
32
40
48
56
64
72
80
88
96
104
WEEKS OF EXPOSURE
100 PPM
33 PPM
10 PPM
CONTROL I
CONTROL II

Figure 4

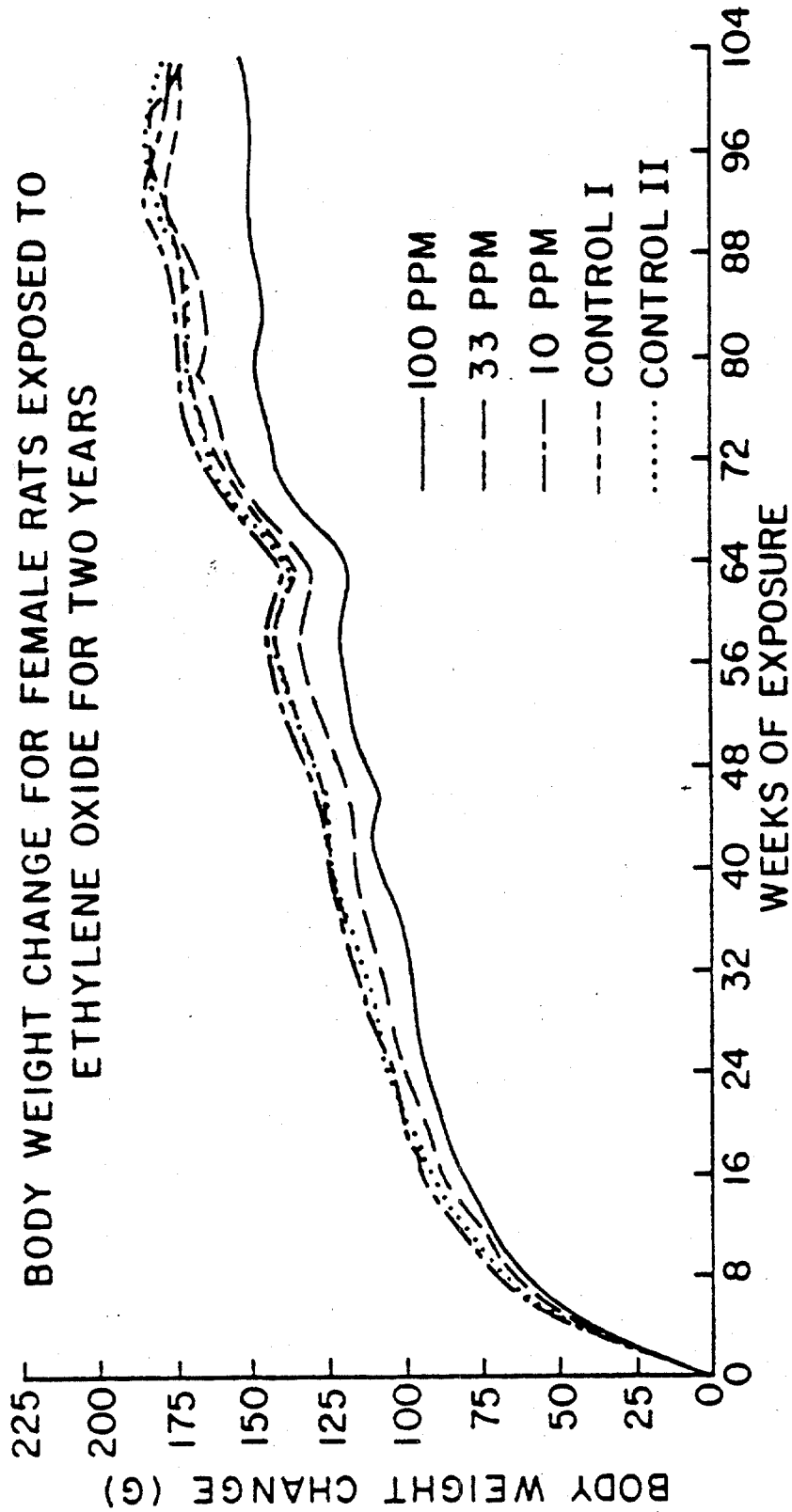
BODY WEIGHT CHANGE FOR FEMALE RATS EXPOSED TO ETHYLENE OXIDE FOR TWO YEARS
BODY WEIGHT CHANGE (G)
225
200
175
150
125
100
75
50
25
0
0
8
16
24
32
40
48
56
64
72
80
88
96
104
WEEKS OF EXPOSURE
100 PPM
33 PPM
10 PPM
CONTROL I
CONTROL II

Figure 5

when compared to both Air Control groups, was first observed at the end of the 10th exposure week (48 exposures completed). This statistically significant difference continued until the "recovery period" from the SDA virus infection, after which time the mean values of this group remained lower, but only sporadic statistical significances were observed. After 18 months of exposure, the meaningful interpretation of the body weight data is questionable because the normal increase in spontaneously occurring tumors significantly affects the body weight.

Presented in Figures 6 and 7 are more detailed graphs, better depicting the differences between groups for male and female rats, respectively. The period of time in these figures encompasses the SDA virus infection and "recovery" periods. During the infection period, the body weight was markedly depressed similarly for all groups. Proportionately, the males lost more body weight than the females. Following the "recovery" period, all groups appeared to return to their preinfection rate of body weight gain.

Ophthalmologic Examinations

The veterinary ophthalmologist's report is in Appendix III. In his report, the summary observations were not separated according to sex, nor were there any statistical analyses performed. Presented in Tables 14 and 15 are the ophthalmologic findings which are separated by sex, males and females, respectively, and analyzed for statistical significance. No significant differences were noted.

Certain eye lesions which were present in all groups in the 18- and 24-month observation intervals may be representative of the same pathogenetic mechanism associated with the SDA virus infection. Consequently, possible interrelated abnormalities were combined, and the results are presented in Table 16. Again, no significant differences were noted.

It was concluded, in the ophthalmologist's report, that, in view of the confirmed SDA virus infection, the ocular abnormalities observed in this study had no apparent toxicologic relationship to EO.

Urinalysis

Presented in Tables 17 and 18 are the summary results of the routine urinalysis determinations for male and female rats, respectively, sacrificed after 6, 12, 18 and 24 months of exposure. The individual routine urinalysis values of each group are reported in Appendix V, Tables A-18 through A-25, for all sacrifice intervals. By inspection of the results for the male and female rats, there were no apparent differences that would indicate a treatment-related effect at any of the four sacrifice intervals.

The summaries of the microscopic urinalysis results at the 6-, 12-, 18- and 24-month sacrifice intervals are presented in Tables 19 and 20 for male and female rats, respectively. Reported in Appendix V, Tables A-26 through A-33,

Table 14
Ophthalmologic Findings[1] at 6-Month Intervals
from Male Rats Exposed to Ethylene Oxide
by Inhalation for Two Years

	Exposure Interval			
	6-Month	12-Month	18-Month	24-Month
CATEGORY A				
100 ppm	0/10	0/10	1/20	0/41
33 ppm	1/10	1/10	0/20	0/46
10 ppm	2/10	0/10	0/20	0/62
Control I	0/10	0/10	0/20	0/57
Control II	0/10	0/10	0/20	0/66
CATEGORY B				
100 ppm	0/10	0/10	1/20	0/41
33 ppm	0/10	0/10	0/20	1/46
10 ppm	0/10	1/10	0/20	1/62
Control I	0/10	0/10	0/20	0/57
Control II	1/10	0/10	1/20	0/66
CATEGORY C				
100 ppm	0/10	0/10	1/20	3/41
33 ppm	1/10	0/10	3/20	1/46
10 ppm	0/10	0/10	1/20	3/62
Control I	0/10	0/10	0/20	3/57
Control II	0/10	1/10	2/20	2/66
CATEGORY D				
100 ppm	0/10	0/10	0/20	0/41
33 ppm	0/10	1/10	0/20	1/46
10 ppm	0/10	1/10	0/20	4/62
Control I	0/10	1/10	1/20	4/57
Control II	0/10	0/10	0/20	2/66
CATEGORY E				
100 ppm	0/10	0/10	0/20	0/41
33 ppm	0/10	0/10	0/20	0/46
10 ppm	0/10	0/10	0/20	0/62
Control I	0/10	0/10	1/20	1/57
Control II	0/10	1/10	0/20	1/66
CATEGORY F				
100 ppm	0/10	0/10	0/20	2/41
33 ppm	0/10	0/10	0/20	2/46
10 ppm	0/10	0/10	0/20	4/62
Control I	0/10	0/10	0/20	1/57
Control II	0/10	0/10	1/20	0/66

[1]Categories defined by Dr. R. W. Bellhorn. Refer to Appendix III for an in-depth description of each category. The numerator is the number of rats with the lesion and the denominator is the number of rats examined.

Category A = Congenital defects
Category B = Retinal degeneration
Category C = Sialodacryoadenitis complex
Category D = Lens abnormalities
Category E = Phthisis bulbi
Category F = Miscellaneous findings

Table 15
Ophthalmologic Findings[1] at 6-Month Intervals
from Female Rats Exposed to Ethylene Oxide
by Inhalation for Two Years

	Exposure Interval			
	6-Month	12-Month	18-Month	24-Month
CATEGORY A				
100 ppm	2/10	0/10	0/20	0/34
33 ppm	0/10	0/10	0/20	0/52
10 ppm	0/10	0/10	0/20	0/59
Control I	1/10	0/10	0/19	0/63
Control II	1/10	0/10	0/20	0/57
CATEGORY B				
100 ppm	0/10	0/10	0/20	1/34
33 ppm	0/10	0/10	0/20	0/52
10 ppm	0/10	0/10	0/20	0/59
Control I	0/10	0/10	0/19	0/63
Control II	0/10	0/10	0/20	0/57
CATEGORY C				
100 ppm	0/10	0/10	2/20	6/34
33 ppm	0/10	0/10	4/20	8/52
10 ppm	0/10	0/10	4/20	4/59
Control I	0/10	0/10	1/19	10/63
Control II	1/10	0/10	3/20	6/57
CATEGORY D				
100 ppm	0/10	0/10	1/20	5/34
33 ppm	0/10	0/10	0/20	1/52
10 ppm	0/10	1/10	1/20	0/59
Control I	0/10	1/10	0/19	2/63
Control II	0/10	1/10	0/20	1/57
CATEGORY E				
100 ppm	0/10	0/10	1/20	2/34
33 ppm	0/10	0/10	0/20	3/52
10 ppm	0/10	0/10	0/20	6/59
Control I	0/10	0/10	0/19	2/63
Control II	0/10	0/10	0/20	1/57
CATEGORY F				
100 ppm	0/10	0/10	0/20	1/34
33 ppm	0/10	0/10	0/20	2/52
10 ppm	0/10	0/10	0/20	1/59
Control I	0/10	0/10	0/19	1/63
Control II	0/10	0/10	0/20	1/57

[1]Categories defined by Dr. R. W. Bellhorn. Refer to Appendix III for an in-depth description of each category. The numerator is the number of rats with the lesion and the denominator is the number of rats examined.

Category A = Congenital defects
Category B = Retinal degeneration
Category C = Sialodacryoadenitis complex
Category D = Lens abnormalities
Category E = Phthisis bulbi
Category F = Miscellaneous findings

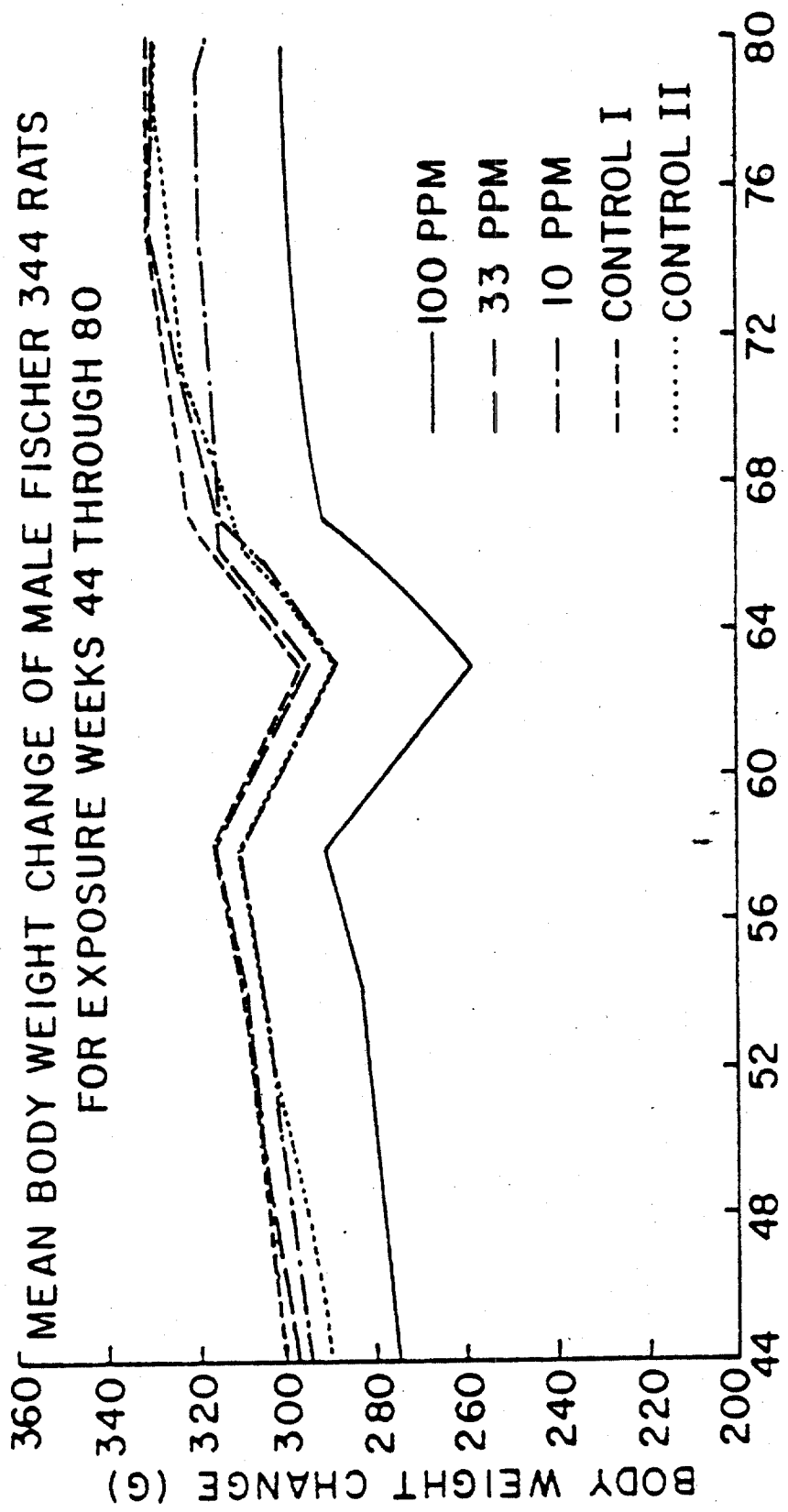
MEAN BODY WEIGHT CHANGE OF MALE FISCHER 344 RATS
FOR EXPOSURE WEEKS 44 THROUGH 80
BODY WEIGHT CHANGE (G)
360
340
320
300
280
260
240
220
200
44
48
52
56
60
64
68
72
76
80
WEEKS OF EXPOSURE
100 PPM
33 PPM
10 PPM
CONTROL I
CONTROL II

Figure 6

Figure 7

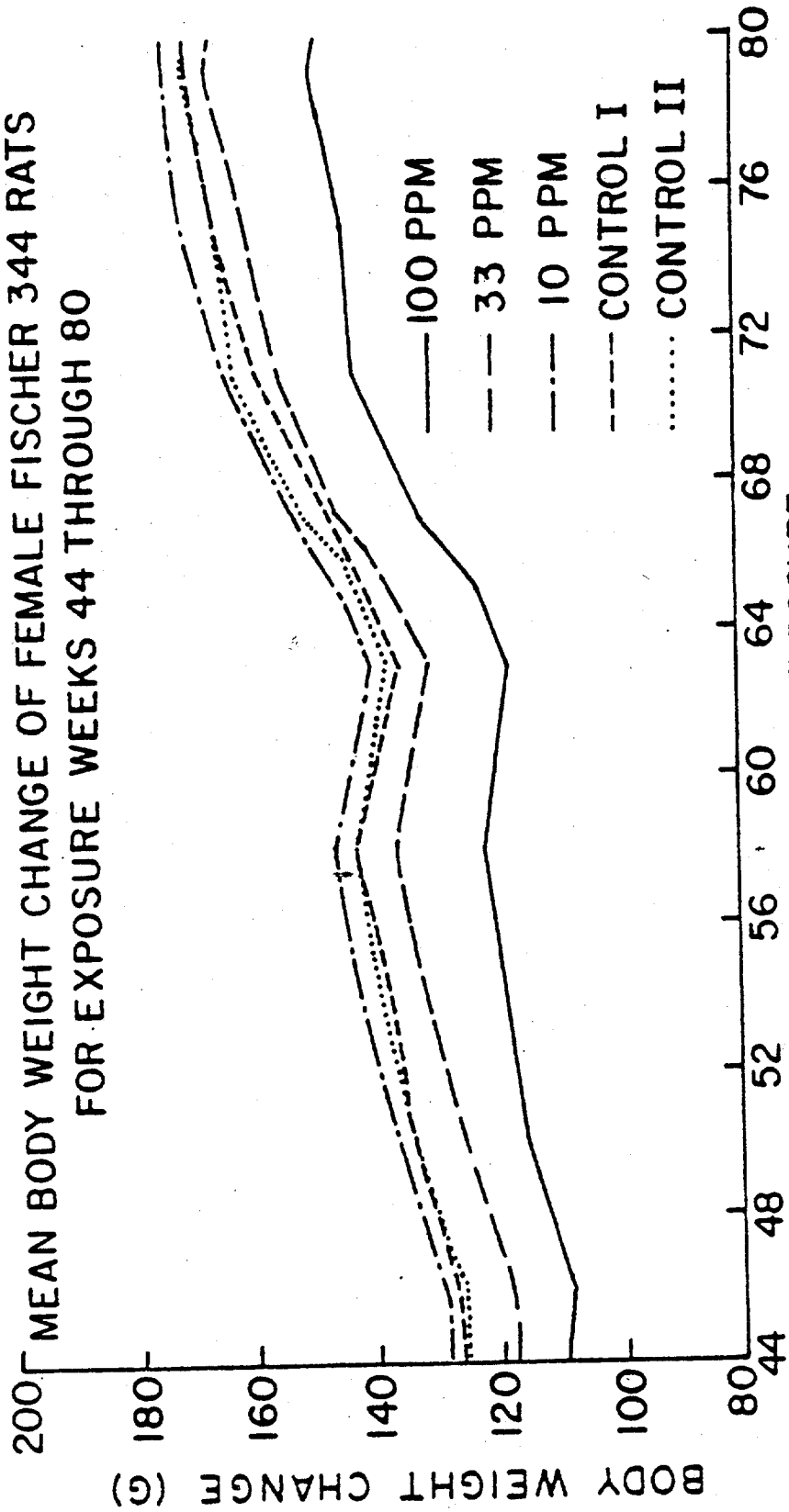
MEAN BODY WEIGHT CHANGE OF FEMALE FISCHER 344 RATS
FOR EXPOSURE WEEKS 44 THROUGH 80
BODY WEIGHT CHANGE (G)
200
180
160
140
120
100
80
44
48
52
56
60
64
68
72
76
80
WEEKS OF EXPOSURE
100 PPM
33 PPM
10 PPM
CONTROL I
CONTROL II

Table 14
Ophthalmologic Findings[1] at 6-Month Intervals
from Male Rats Exposed to Ethylene Oxide
by Inhalation for Two Years

	Exposure Interval			
	6-Month	12-Month	18-Month	24-Month
CATEGORY A				
100 ppm	0/10	0/10	1/20	0/41
33 ppm	1/10	1/10	0/20	0/46
10 ppm	2/10	0/10	0/20	0/62
Control I	0/10	0/10	0/20	0/57
Control II	0/10	0/10	0/20	0/66
CATEGORY B				
100 ppm	0/10	0/10	1/20	0/41
33 ppm	0/10	0/10	0/20	1/46
10 ppm	0/10	1/10	0/20	1/62
Control I	0/10	0/10	0/20	0/57
Control II	1/10	0/10	1/20	0/66
CATEGORY C				
100 ppm	0/10	0/10	1/20	3/41
33 ppm	1/10	0/10	3/20	1/46
10 ppm	0/10	0/10	1/20	3/62
Control I	0/10	0/10	0/20	3/57
Control II	0/10	1/10	2/20	2/66
CATEGORY D				
100 ppm	0/10	0/10	0/20	0/41
33 ppm	0/10	1/10	0/20	1/46
10 ppm	0/10	1/10	0/20	4/62
Control I	0/10	1/10	1/20	4/57
Control II	0/10	0/10	0/20	2/66
CATEGORY E				
100 ppm	0/10	0/10	0/20	0/41
33 ppm	0/10	0/10	0/20	0/46
10 ppm	0/10	0/10	0/20	0/62
Control I	0/10	0/10	1/20	1/57
Control II	0/10	1/10	0/20	1/66
CATEGORY F				
100 ppm	0/10	0/10	0/20	2/41
33 ppm	0/10	0/10	0/20	2/46
10 ppm	0/10	0/10	0/20	4/62
Control I	0/10	0/10	0/20	1/57
Control II	0/10	0/10	1/20	0/66

[1]Categories defined by Dr. R. W. Bellhorn. Refer to Appendix III for an in-depth description of each category. The numerator is the number of rats with the lesion and the denominator is the number of rats examined.

Category A = Congenital defects
Category B = Retinal degeneration
Category C = Sialodacryoadenitis complex
Category D = Lens abnormalities
Category E = Phthisis bulbi
Category F = Miscellaneous findings

Table 15
Ophthalmologic Findings[1] at 6-Month Intervals
from Female Rats Exposed to Ethylene Oxide
by Inhalation for Two Years

	Exposure Interval			
	6-Month	12-Month	18-Month	24-Month
CATEGORY A				
100 ppm	2/10	0/10	0/20	0/34
33 ppm	0/10	0/10	0/20	0/52
10 ppm	0/10	0/10	0/20	0/59
Control I	1/10	0/10	0/19	0/63
Control II	1/10	0/10	0/20	0/57
CATEGORY B				
100 ppm	0/10	0/10	0/20	1/34
33 ppm	0/10	0/10	0/20	0/52
10 ppm	0/10	0/10	0/20	0/59
Control I	0/10	0/10	0/19	0/63
Control II	0/10	0/10	0/20	0/57
CATEGORY C				
100 ppm	0/10	0/10	2/20	6/34
33 ppm	0/10	0/10	4/20	8/52
10 ppm	0/10	0/10	4/20	4/59
Control I	0/10	0/10	1/19	10/63
Control II	1/10	0/10	3/20	6/57
CATEGORY D				
100 ppm	0/10	0/10	1/20	5/34
33 ppm	0/10	0/10	0/20	1/52
10 ppm	0/10	1/10	1/20	0/59
Control I	0/10	1/10	0/19	2/63
Control II	0/10	1/10	0/20	1/57
CATEGORY E				
100 ppm	0/10	0/10	1/20	2/34
33 ppm	0/10	0/10	0/20	3/52
10 ppm	0/10	0/10	0/20	6/59
Control I	0/10	0/10	0/19	2/63
Control II	0/10	0/10	0/20	1/57
CATEGORY F				
100 ppm	0/10	0/10	0/20	1/34
33 ppm	0/10	0/10	0/20	2/52
10 ppm	0/10	0/10	0/20	1/59
Control I	0/10	0/10	0/19	1/63
Control II	0/10	0/10	0/20	1/57

[1]Categories defined by Dr. R. W. Bellhorn. Refer to Appendix III for an in-depth description of each category. The numerator is the number of rats with the lesion and the denominator is the number of rats examined.

Category A = Congenital defects
Category B = Retinal degeneration
Category C = Sialodacryoadenitis complex
Category D = Lens abnormalities
Category E = Phthisis bulbi
Category F = Miscellaneous findings

Table 16
Ophthalmologic Findings[1] That May Be Interrelated from
Male and Female Rats Exposed to Ethylene Oxide
by Inhalation for Two Years

	Exposure Interval			
	6-Month	12-Month	18-Month	24-Month
Male				
CATEGORY C,D,E				
100 ppm	0/10	0/10	1/20	3/41
33 ppm	1/10	1/10	3/20	2/46
10 ppm	0/10	1/10	1/20	7/62
Control I	0/10	1/10	2/20	8/57
Control II	0/10	2/10	2/20	5/66
Female				
CATEGORY C,D,E				
100 ppm	0/10	0/10	4/20	13/34
33 ppm	0/10	0/10	4/20	12/52
10 ppm	0/10	1/10	5/20	10/59
Control I	0/10	1/10	1/19	14/63
Control II	1/10	1/10	3/20	8/57

[1]These categories were combined because they may be representative of the same pathogenetic mechanism of the sialodacryoadenitis virus infection. For further details refer to Appendix III. The numerator is the number of rats with the lesion and the denominator is the number of rats examined.

Category C = Sialodacryoadenitis complex
Category D = Lens abnormalities
Category E = Phthisis bulbi

WPC/1062

Table 17

Summary Values of Urinalysis Determinations for Male Rats Exposed to Ethylene Oxide Vapor

Exposure Concentration	N	Specific Gravity $\bar{X}$ ± SD		pH Q_2	pH QD	Protein Q_2	Protein QD	Occult Blood Q_2	Occult Blood QD	Urobilinogen Q_2	Urobilinogen QD
6 Months of Exposure											
100 ppm	10	1.030	0.022	7.0	0.5	0.2	0.2	0.0	0.0	0.1	0.0
33 ppm	10	1.038	0.016	8.0	0.5	0.0	0.2	0.0	0.0	0.1	0.0
10 ppm	9	1.021[-,a]	0.006	8.0	0.2	0.0	0.1	0.0	0.0	0.1	0.0
0 ppm (CI)	10	1.042	0.029	8.0	0.0	0.5	0.5	0.0	0.0	0.1	0.0
0 ppm (CII)	10	1.041	0.018	8.0	0.5	0.0	0.3	0.0	0.0	0.1	0.0
12 Months of Exposure											
100 ppm	10	1.021	0.012	8.0	0.5	1.0	0.1	0.0	0.5	0.1	0.0
33 ppm	9	1.020	0.004	8.0	0.5	1.0	0.5	0.0	0.0	0.1	0.0
10 ppm	10	1.025	0.018	8.0	0.5	1.0	0.5	0.5	1.0	0.1	0.0
0 ppm (CI)	10	1.024	0.004	7.0	0.5	2.0	0.1	0.0	0.0	0.1	0.0
0 ppm (CII)	10	1.024	0.010	8.0	0.5	2.0	0.5	0.0	0.1	0.1	0.0
18 Months of Exposure											
100 ppm	18	1.027	0.021	8.0	0.5	3.0	0.5	0.0	0.0	0.1	0.0
33 ppm	20	1.035	0.020	8.0	0.5	3.0	0.5	0.0	0.0	0.1	0.0
10 ppm	20	1.029	0.012	8.0	0.5	3.0	0.4	0.0	0.0	0.1	0.0
0 ppm (CI)	20	1.027	0.011	8.0	0.0	3.0	0.5	0.0	0.0	0.1	0.0
0 ppm (CII)	18	1.035	0.016	8.0	0.5	3.0	0.0	0.0	0.0	0.1	0.4
24 Months of Exposure											
100 ppm	19	1.038	0.015	6.0	0.5	4.0	1.0	1.0	0.5	0.1	0.0
33 ppm	20	1.040	0.016	7.0	0.0	4.0	0.5	0.0	0.8	0.1	0.0
10 ppm	19	1.039	0.012	7.0	0.0	4.0	0.2	0.5	0.5	0.1	0.0
0 ppm (CI)	19	1.037	0.015	7.0	0.0	4.0	0.0	0.0	0.5	0.1	0.0
0 ppm (CII)	20	1.048	0.020	7.0	0.5	4.0	0.0	0.0	0.5	0.1	0.0

a = $0.05 > p > 0.01$

Statistical comparisons were performed for only specific gravity.

First letter of superscript denotes degree of significance vs. Air Control I (CI); second letter denotes degree of significance vs. Air Control II (CII).

N = Number of samples analyzed for most parameters. In certain cases quantity was not sufficient for individual determinations.

Mean ($\bar{X}$) and standard deviation (SD) are expressed for specific gravity. Median (Q_2) and quartile deviation (QD) are expressed for all other parameters. The Q_2 and QD for glucose, ketone, bilirubin and nitrite were all 0.0 except ketone which had a QD of 0.4 for 33 ppm at 18 months.

Ames N-MULTISTIX® units:
pH: 5; 6; 7; 8; 9
Protein: 0 = negative; ± = trace; 1+ = 30 mg/dL; 2+ = 100 mg/dL; 3+ = 500 mg/dL; 4+ = > 2000 mg/dL
Blood: 0 = negative; 1+ = small; 2+ = moderate; 3+ = large
Urobilinogen: 0.1 and 1.0 Erlich units/dL = normal; 2, 4, 8 12 Erlich units/dL

Table 18
Summary Values of Urinalysis Determinations
for Female Rats Exposed to Ethylene Oxide Vapor

Exposure Concentration	N	Specific Gravity $\bar{X}$ ± SD		pH		Protein		Occult Blood		Urobilinogen	
				Q_2	QD	Q_2	QD	Q_2	QD	Q_2	QD
6 Months of Exposure											
100 ppm	8	1.044	0.016	8.5	0.5	0.0	0.0	0.0	0.0	0.1	0.0
33 ppm	8	1.050	0.011	8.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0
10 ppm	9	1.064	0.031	8.0	1.0	0.0	0.5	0.0	0.0	0.1	0.0
0 ppm (CI)	10	1.060	0.018	7.5	0.5	0.0	0.6	0.0	0.0	0.1	0.0
0 ppm (CII)	6	1.050	0.014	7.0	0.6	0.0	0.3	0.0	0.0	0.1	0.0
12 Months of Exposure											
100 ppm	10	1.024	0.007	8.0	0.5	1.0	0.8	0.0	0.0	0.1	0.0
33 ppm	9	1.027	0.009	7.0	0.5	1.0	0.0	0.0	0.0	0.1	0.0
10 ppm	7	1.028	0.016	7.0	0.5	1.0	0.5	0.0	0.0	0.1	0.0
0 ppm (CI)	8	1.036	0.014	7.5	0.5	1.5	0.5	0.0	0.4	0.1	0.0
0 ppm (CII)	9	1.029	0.011	8.0	0.0	1.0	0.5	0.0	0.0	0.1	0.0
18 Months of Exposure											
100 ppm	16	1.026	0.013	8.0	0.4	1.0	0.4	0.0	0.0	0.1	0.0
33 ppm	16	1.026	0.018	8.0	0.5	1.0	0.5	0.0	0.0	0.1	0.0
10 ppm	17	1.029	0.013	8.0	0.5	2.0	0.5	0.0	0.0	0.1	0.0
0 ppm (CI)	14	1.028	0.016	8.0	0.0	2.0	0.6	0.0	0.0	0.1	0.1
0 ppm (CII)	13	1.038	0.019	8.0	0.2	2.0	1.0	0.0	0.0	0.1	0.4
24 Months of Exposure											
100 ppm	19	1.050	0.016	7.0	1.0	2.0	1.4	0.0	0.0	0.1	0.0
33 ppm	17	1.054	0.020	7.0	1.0	3.0	0.5	0.0	0.0	0.1	0.0
10 ppm	17	1.046	0.016	7.0	0.8	3.0	1.0	0.0	0.0	0.1	0.0
0 ppm (CI)	17	1.053	0.016	7.0	0.8	4.0	0.5	0.0	0.0	0.1	0.0
0 ppm (CII)	15	1.052	0.020	7.0	0.0	3.0	0.8	0.0	0.0	0.1	0.0

Statistical comparisons were performed for only specific gravity.

N = Number of samples analyzed for most parameters. In certain cases quantity was not sufficient for individual determinations.

Mean ($\bar{X}$) and standard deviation (SD) are expressed for specific gravity. Median (Q_2) and quartile deviation (QD) are expressed for all other parameters. The Q_2 and QD for glucose, ketone, bilirubin and nitrite were all 0.0 except ketone which had a QD of 0.4 for 33 ppm at 18 months.

Ames N-MULTISTIX® units:
pH: 5; 6; 7; 8; 9
Protein: 0 = negative; + = trace; 1+ = 30 mg/dL; 2+ = 100 mg/dL; 3+ = 500 mg/dL; 4+ = > 2000 mg/dL
Blood: 0 = negative; 1+ = small; 2+ = moderate; 3+ = large
Urobilinogen: 0.1 and 1.0 Ehrlich units/dL = normal; 2, 4, 8 12 Ehrlich units/dL

Table 19

Summary Values of Microscopic Urinalysis Determinations
for Male Rats Exposed to Ethylene Oxide Vapor

Exposure Concentration	N	Crystals: Triple Phosphate Q_2	Crystals: Triple Phosphate QD	Cells: Spermatozoa Q_2	Cells: Spermatozoa QD	Cells: Epithelial Q_2	Cells: Epithelial QD	Cells: White Blood Cells Q_2	Cells: White Blood Cells QD	Cast: Hyaline Q_2	Cast: Hyaline QD
6 Months of Exposure											
100 ppm	10	0.5	0.8	2.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0
33 ppm	10	2.0	0.6	1.0	1.1	0.0	0.0	0.0	0.0	0.0	0.0
10 ppm	9	1.0	0.5	0.0	0.8	0.0	0.0	0.0	0.0	0.0	0.0
0 ppm (CI)	10	1.0	1.1	1.0	0.8	0.0	0.0	0.0	0.0	0.0	0.0
0 ppm (CII)	10	1.5	1.5	1.5	1.0	0.0	0.0	0.0	0.0	0.0	0.0
12 Months of Exposure											
100 ppm	9	1.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
33 ppm	9	1.0	1.0	0.0	1.5	0.0	0.0	0.0	0.0	0.0	0.0
10 ppm	10	0.5	1.0	1.0	1.5	0.0	0.0	0.0	0.0	0.0	0.0
0 ppm (CI)	10	1.0	1.0	1.0	1.5	0.0	0.1	0.0	0.0	0.0	0.0
0 ppm (CII)	9	1.0	1.0	1.5	0.9	0.0	0.2	0.0	0.0	0.0	0.0
18 Months of Exposure											
100 ppm	18	1.0	1.0	0.0	0.5	0.0	0.0	0.0	0.0	0.0	0.0
33 ppm	19	1.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
10 ppm	20	1.5	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0 ppm (CI)	20	1.5	0.9	0.0	0.4	0.0	0.0	0.0	0.0	0.0	0.0
0 ppm (CII)	17	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
24 Months of Exposure											
100 ppm	18	0.0	0.0	0.0	0.0	0.0	0.5	0.0	0.5	0.0	0.5
33 ppm	20	0.0	0.5	0.0	0.0	0.0	0.5	0.0	0.0	0.0	0.5
10 ppm	18	0.0	0.5	0.0	0.1	0.0	0.1	0.0	0.1	0.0	0.1
0 ppm (CI)	19	0.0	0.0	0.0	0.0	0.0	0.5	0.0	0.0	0.0	0.5
0 ppm (CII)	17	0.0	0.5	0.0	0.2	0.0	0.5	1.0	0.5	1.0	0.5

No statistical comparisons were performed for any parameter.

N = Number of samples analyzed

Median (Q_2) and quartile deviation (QD) are expressed for all parameters. Calcium oxylate and amorphous crystals always had Q_2 and QD values of 0.0. Red blood cells always had a Q_2 of 0.0 and a QD of less than 0.2.

Units: 0 = negative; 1 = a few; 2 = moderate amount; 3 = numerous.

Table 20

Summary Values of Microscopic Urinalysis Determinations for Female Rats Exposed to Ethylene Oxide Vapor

Exposure Concentration	N	Crystals: Triple Phosphate Q_2	Crystals: Triple Phosphate QD	Crystals: Amorphous Q_2	Crystals: Amorphous QD	Cells: Epithelial Q_2	Cells: Epithelial QD	Cells: White Blood Cells Q_2	Cells: White Blood Cells QD
6 Months of Exposure									
100 ppm	8	1.0	0.8	1.5	0.9	0.0	0.4	0.0	0.0
33 ppm	6	1.5	0.6	0.5	0.6	0.0	0.1	0.0	0.1
10 ppm	7	1.0	0.5	0.0	0.0	0.0	0.0	0.0	0.0
0 ppm (CI)	8	1.5	0.5	0.0	0.4	0.0	0.0	0.0	0.0
0 ppm (CII)	5	1.0	0.5	0.0	0.5	0.0	0.2	0.0	0.2
12 Months of Exposure									
100 ppm	10	0.0	0.5	0.0	0.0	0.0	0.0	0.0	0.0
33 ppm	8	1.0	0.9	0.0	0.0	0.0	0.4	0.0	0.0
10 ppm	7	0.0	0.5	0.0	0.0	0.0	0.5	0.0	0.0
0 ppm (CI)	7	1.0	0.5	0.0	0.0	0.0	0.5	0.0	0.0
0 ppm (CII)	9	1.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0
18 Months of Exposure									
100 ppm	15	1.0	0.5	1.0	0.5	0.0	0.0	0.0	0.0
33 ppm	13	0.0	0.5	0.0	0.8	0.0	0.2	0.0	0.0
10 ppm	16	1.0	1.0	0.5	0.5	0.0	0.0	0.0	0.0
0 ppm (CI)	12	1.0	1.0	0.5	0.5	0.0	0.4	0.0	0.0
0 ppm (CII)	10	1.0	1.0	0.5	0.6	0.0	0.0	0.0	0.0
24 Months of Exposure									
100 ppm	17	0.0	0.5	0.0	0.0	0.0	0.0	0.0	0.0
33 ppm	15	0.0	0.5	0.0	0.0	0.0	0.0	0.0	0.0
10 ppm	16	0.0	0.5	0.5	0.9	0.0	0.0	0.0	0.4
0 ppm (CI)	16	0.0	0.5	1.0	0.9	0.0	0.0	0.0	0.0
0 ppm (CII)	15	0.0	0.5	0.0	0.5	0.0	0.0	0.0	0.0

No statistical comparisons were made for any parameter.

N = Number of samples analyzed

Median (Q_2) and quartile deviation (QD) are expressed for all parameters. Hyaline casts, red blood cells, calcium oxylate and amorphous crystals always had Q_2 and QD values of 0.0.

Units: 0 = negative; 1 = a few; 2 = moderate amount; 3 = numerous.

are the individual animal microscopic urinalysis values for all groups at each sacrifice interval. No apparent differences that would indicate a treatment-related effect at any of the four sacrifice intervals were noted by inspection of the data for either the male or female rats.

Routine Hematology with Leukocyte Differential Evaluation

The summary values of the routine hematologic determinations for each of the four sacrifice intervals are presented in Tables 21 and 22 for male and female rats, respectively, and the leukocyte differential counts are in Tables 23 and 24 for males and 25 and 26 for females. All individual routine hematology values of each group are contained in Appendix VI, Tables A-34 through A-37 for males and Tables A-38 through A-41 for females, and all leukocyte differential values are in Appendix VI, Tables A-42 through A-45 for the males and in Tables A-46 through A-49 for the females.

The hematologic results for the 24-month interval are presented two ways: with all values included in the statistical analysis, and with the values from animals with histologically confirmed mononuclear cell leukemia removed from the analysis. The elimination process was performed because leukemia, which occurred only after the previous hematologic assessment at 18 months, represents a confounding variable in the hematologic evaluation. Mononuclear cell leukemia was observed in all groups, but the frequency was increased in the 100 ppm group, especially for female rats. It is pointed out that histologic confirmation was required before the final resolution of whether or not an animal had leukemia was made. [Note: There was substantial agreement between the hematologic and histologic evaluations. There were false positives only 2.1% of the time (males and females combined); that is, 2.1% of the animals with positive hematologic diagnoses were negative by histologic diagnoses. The diagnosis for mononuclear cell leukemia was negative hematologically 9.4% of the time when it was positive histologically. This was probably because blood samples were obtained a few weeks before sacrifice, therefore, allowing time for new cases of leukemia to develop.] The blood values of the rats with leukemia are indicated in Appendix VI, Table A-45 for males and Table A-49 for females.

Males

There were no dose-related effects for any hematologic parameters that were indicative of a toxicologic effect at the 6- or 12-month intervals. At the 6-month interval, the mean values for a few of the parameters of the leukocyte differential count were statistically significantly different from those of one control group. However, these differences are not considered to be of toxicologic significance because, in most of these cases, the mean values of the two control groups were also significantly different from each other.

At the 18-month sacrifice period the only statistically significant difference was a lower mean absolute neutrophil count of the 100 ppm group; the biological significance of this finding is unknown.

At the 24-month sacrifice interval, with or without removing the values of the animals with leukemia from statistical analysis, the total leukocyte count

Table 21

Summary Values of Hematologic Determinations for Male Rats Exposed to Ethylene Oxide Vapor

Exposure Concentration	N	Red Blood Cells ($\times 10^6/mm^3$) $\bar{X} \pm SD$		Hematocrit (%) Q_2	QD	Hemoglobin (g/dL) $\bar{X} \pm SD$		Mean Corpuscular Volume (μ^3) Q_2	QD	Mean Corpuscular Hemoglobin (μμg) Q_2	QD	Mean Corpuscular Hemoglobin Concentration (%) Q_2	QD	White Blood Cells ($/mm^3$) $\bar{X} \pm SD$		Blood Clotting Time (seconds) $\bar{X} \pm SD$	
6 Months of Exposure																	
100 ppm	10	6.57	0.19	35.5	1.0	15.1	0.3	55.0	0.5	23.0	0.5	42.0	1.0	4300	500	132	17
33 ppm	10	6.61	0.20	36.0	1.0	15.1	0.3	55.0	0.5	23.0	0.5	42.0	1.0	3800[a,-]	500	123	15
10 ppm	10	6.54	0.15	36.0	1.0	14.9	0.4	55.0	0.5	23.0	0.1	42.0	0.1	3700[b,-]	800	119	31
0 ppm (CI)	10	6.59	0.14	36.0	0.6	15.1	0.4	55.0	0.5	23.0	0.2	42.0	0.6	4700	900	127	24
0 ppm (CII)	10	6.57	0.23	35.0	0.6	14.9	0.3	55.0	0.5	23.0	0.5	42.0	1.0	4400	900	134	22
12 Months of Exposure																	
100 ppm	10	7.51	0.25	40.5	1.6	14.6	0.5	54.0	0.5	19.5	0.5	36.0	1.1	3500	1000	119	33
33 ppm	10	7.72	0.20	42.0	1.0	14.9	0.3	54.0	0.6	19.0	0.1	36.0	0.6	3600	500	112	14
10 ppm	10	7.58	0.30	42.0	2.0	14.6	0.5	54.5	1.2	19.0	0.5	35.5	1.5	4100	1600	117	25
0 ppm (CI)	10	7.58	0.19	41.0	1.0	14.7	0.4	54.0	0.4	19.5	0.5	35.5	1.0	3900	1400	104	41
0 ppm (CII)	10	7.49	0.16	40.5	0.6	14.5	0.4	54.0	0.5	19.0	0.5	36.0	0.6	3500	1100	125	34
18 Months of Exposure																	
100 ppm	20	8.57	0.29	43.0	0.5	14.8	0.4	51.0	0.0	17.0	0.0	34.0	0.5	3000	800	130	40
33 ppm	20	8.57	0.36	43.5	1.0	15.0	0.6	52.0	0.9	17.5	0.5	34.0	0.5	3600	1000	160	45
10 ppm	20	8.75	0.78	44.0	1.4	15.3	1.5	52.0	0.5	17.5	0.5	34.0	0.4	3300	900	138	50
0 ppm (CI)	20	8.79	0.77	44.0	1.2	15.5	1.5	52.0	0.9	17.0	0.9	34.0	0.5	3900	900	158	54
0 ppm (CII)	20	8.69	0.63	43.0	1.0	15.1	1.1	51.0	0.9	17.0	0.5	34.0	0.5	3500	1400	129	50
24 Months of Exposure (All values were included in statistical analysis)																	
100 ppm	20	7.16	2.25	40.5	7.2	14.8	3.8	55.0	4.8	20.5	1.0	37.0	2.0	25600	41800	-[A]	-
33 ppm	20	7.38	1.97	44.5	5.9	15.5	3.2	56.0	3.5	21.0	1.4	37.0	2.4	11800	13700	-	-
10 ppm	18	7.50	2.09	41.0	6.0	15.5	3.6	54.0	2.0	20.0	0.5	38.0	1.2	12500	23400	-	-
0 ppm (CI)	20	7.98	1.63	45.0	5.5	16.4	3.0	55.0	2.8	20.0	0.9	37.5	2.8	13400	21400	-	-
0 ppm (CII)	18	7.19	1.64	40.0	4.0	14.8	3.0	55.0	3.0	20.5	1.0	37.0	2.1	13000	12700	-	-
24 Months of Exposure (Values from animals with leukemia were removed from statistical analysis)																	
100 ppm	14	7.63	2.12	41.0	7.2	15.6	3.9	54.5	1.9	20.0	0.8	38.0	1.2	12900	19200	-[A]	-
33 ppm	12	8.11	1.40	45.0	3.8	16.5	2.6	55.5	2.4	20.5	0.9	37.0	2.4	7000	3600	-	-
10 ppm	13	8.02	1.51	41.0	6.5	16.6	2.9	54.0	2.0	20.0	0.5	39.0	1.0	6300	2000	-	-
0 ppm (CI)	18	8.21	1.53	47.5	5.6	16.8	3.0	54.5	2.5	20.0	0.6	38.0	2.6	7200	3800	-	-
0 ppm (CII)	14	7.60	1.49	41.0	4.0	15.5	2.8	55.0	0.6	20.0	0.6	38.5	1.6	9100	5400	-	-

a = $0.05 > p > 0.01$ b = $0.01 > p > 0.001$

First letter of superscript denotes degree of significance vs. Air Control I (CI); second letter denotes degree of significance vs. Air Control II (CII). No statistical comparisons were made for hematocrit, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration.

N = Number of samples analyzed.

Mean ($\bar{X}$) and standard deviation (SD) are expressed for red blood cells, hemoglobin, white blood cells and blood clotting time. Median (Q_2) and quartile deviation (QD) are expressed for all other parameters.

[A]No determinations were made for this parameter.

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Table 22

Summary Values of Hematologic Determinations for Female Rats Exposed to Ethylene Oxide Vapor

Exposure Concentration	N	Red Blood Cells ($\times 10^6/mm^3$) $\bar{X} \pm SD$		Hematocrit (%) Q_2	QD	Hemoglobin (g/dL) $\bar{X} \pm SD$		Mean Corpuscular Volume (μ^3) Q_2	QD	Mean Corpuscular Hemoglobin ($\mu\mu g$) Q_2	QD	Mean Corpuscular Hemoglobin Concentration (%) Q_2	QD	White Blood Cells ($/mm^3$) $\bar{X} \pm SD$		Blood Clotting Time (seconds) $\bar{X} \pm SD$	
6 Months of Exposure																	
100 ppm	10	7.18	0.33	40.0	1.8	14.6	0.3	56.0	0.5	20.0	0.5	36.5	1.1	3700	700	114	27
33 ppm	10	7.16	0.24	40.0	1.0	14.7	0.3	56.0	0.6	20.5	0.5	37.5	0.8	3900	700	138	21
10 ppm	10	7.26	0.29	40.5	2.0	14.9	0.3	56.0	0.5	20.0	0.5	37.0	1.5	3600	600	112	33
0 ppm (CI)	10	7.22	0.25	39.5	1.5	14.8	0.3	56.0	1.0	20.0	0.5	37.0	0.6	3900	600	126	29
0 ppm (CII)	10	7.20	0.20	39.5	1.0	14.8	0.4	56.0	0.5	20.0	0.5	37.0	1.5	4500	1300	114	33
12 Months of Exposure																	
100 ppm	10	6.88	0.30	38.5	1.2	13.6-,b	0.5	56.5	0.5	20.0	1.0	36.0	1.1	2100	900	125	31
33 ppm	10	7.12	0.38	39.0	2.1	13.9	0.5	57.0	0.9	19.5	0.5	34.0	1.1	2100	500	123	41
10 ppm	10	7.23	0.27	40.0	1.2	14.3	0.3	56.5	0.5	20.0	0.5	35.5	1.5	2400	500	138	43
0 ppm (CI)	10	7.12	0.36	41.0	1.6	14.0	0.6	57.0	0.6	20.0	0.6	34.5	1.8	2400	600	145	13
0 ppm (CII)	10	7.17	0.34	40.0	2.2	14.3	0.3	57.0	0.6	20.0	1.0	35.0	2.1	2800	1000	150	25
18 Months of Exposure																	
100 ppm	19	7.04a,-	0.98	39.0	1.5	13.4a,-	1.8	56.0	0.5	19.0	0.0	35.0	1.0	2500	1500	141	59
33 ppm	20	7.42	0.52	40.5	1.5	14.1	1.0	55.0	0.5	19.0	0.0	35.0	0.5	2800	2400	147	45
10 ppm	18	7.54	0.33	40.5	1.5	14.3	0.7	55.0	0.5	19.0	0.0	35.0	0.1	2100	700	142	50
0 ppm (CI)	20	7.61	0.31	41.0	1.5	14.5	0.6	55.0	0.5	19.0	0.0	35.0	0.5	2200	700	129	49
0 ppm (CII)	18	7.49	0.38	40.0	2.1	14.3	0.7	56.0	0.5	19.0	0.0	35.0	1.0	2200	500	148	40
24 Months of Exposure (All values were included in statistical analysis)																	
100 ppm	18	5.76a,a	1.98	38.0	5.1	12.1a,a	2.8	57.5	12.5	20.0	3.1	35.0	1.5	12600	15300	-*	-
33 ppm	19	6.87	1.69	41.0	2.0	13.7	2.6	57.0	1.0	20.0	0.5	36.0	1.0	6900	9700	-	-
10 ppm	20	7.05	0.99	40.5	2.2	13.8	1.9	56.0	0.5	20.0	0.5	35.0	0.5	6200	6200	-	-
0 ppm (CI)	19	7.02	1.23	41.0	1.5	13.9	1.7	57.0	0.5	20.0	0.5	36.0	0.5	8200	21200	-	-
0 ppm (CII)	19	7.01	1.00	40.0	1.5	14.1	1.4	57.0	0.5	20.0	0.5	36.0	0.5	8900	18100	-	-
24 Months of Exposure (Values from animals with leukemia were removed from statistical analysis)																	
100 ppm	7	7.29	0.47	39.0	1.0	14.4	1.2	57.0	0.5	20.0	0.5	36.0	0.5	4100(a,-)	900	-*	
33 ppm	11	7.50	0.24	41.0	1.0	14.6	0.5	56.0	0.5	20.0	0.5	36.0	0.5	3300	1100	-	
10 ppm	15	7.09	1.14	42.0	2.0	14.0	2.1	56.0	0.5	20.0-	0.5	35.0	0.5	5800	6000	-	
0 ppm (CI)	17	7.33	0.31	41.0	1.5	14.4	0.6	56.0	0.5	20.0	0.5	36.0	0.5	3100	1100		
0 ppm (CII)	16	7.26	0.42	40.0	1.9	14.4	1.0	57.0	0.0	20.0	0.0	36.0	0.5	4000	2500	-	

a = $0.05 > p > 0.01$ b = $0.01 > p > 0.001$

First letter of superscript denotes degree of significance vs. Air Control I (CI); second letter denotes degree of significance vs. Air Control II (CII). No statistical comparisons were made for hematocrit, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration.

N = Number of samples analyzed for most parameters. In certain cases quantity was not sufficient for individual determination.

Mean ($\bar{X}$) and standard deviation (SD) are expressed for red blood cells, hemoglobin, white blood cells and blood clotting time. Median (Q_2) and quartile deviation (QD) are expressed for all other parameters.

*No determinations were made for this parameter.

Table 23

Summary Values[1] of WBC Differential
for Male Rats Exposed to Ethylene Oxide Vapor

Exposure Concentration	N	White Blood Cells ($/mm^3$) $\bar{X}$ + SD	Neutrophils Absolute $\bar{X}$ + SD	Neutrophils (%) $\bar{X}$ + SD	Lymphocytes Absolute $\bar{X}$ + SD	Lymphocytes (%) $\bar{X}$ + SD	Monocytes Absolute Q_2	Monocytes Absolute QD	Monocytes (%) Q_2	Monocytes (%) QD
6 Months of Exposure										
100 ppm	10	4300 500	1400 200	33(b,-) 5	2800a,- 400	65a,- 5	0	18	0.0	0.5
33 ppm	10	3800a,- 500	1100 200	29 5	2700b,- 400	70 5	20	10	0.5	0.5
10 ppm	10	3700b,- 800	1200 300	32 4	2500c,- 500	66a,- 4	0	16	0.0	0.5
0 ppm (CI)	10	4700 900	1200 400	26-,a 8	3400(-,a) 700	72(-,a) 7	0	22	0.0	0.5
0 ppm (CII)	10	4400 900	1500 600	34(a,-) 7	2800a,- 400	64a,- 7	15	24	0.5	0.5
12 Months of Exposure										
100 ppm	10	3500 1000	1900 700	52 8	1600 400	45 7	25	45	1.0	1.1
33 ppm	10	3600 500	1700 500	46 8	1800 300	50 9	70	79	2.0	2.0
10 ppm	10	4100 1600	2000 800	50 9	1900 900	46 10	40	82	1.0	2.2
0 ppm (CI)	10	3900 1400	1900 1000	47 7	1800 400	50 8	45	44	1.5	0.8
0 ppm (CII)	10	3500 1100	1600 700	44 7	1800 500	53 7	35	14	1.0	0.2
18 Months of Exposure										
100 ppm	20	3000 800	1600a,- 600	53 8	1300 400	43 8	60	25	2.0	1.0
33 ppm	20	3600 1000	1800 700	50 7	1600 400	45 7	100	114	3.0	2.4
10 ppm	20	3300 900	1700 600	51 9	1500 400	46 9	55	64	2.0	1.9
0 ppm (CI)	20	3900 900	2000 600	52 9	1700 400	43 8	110	85	3.0	2.0
0 ppm (CII)	20	3500 1400	1900 1200	50 13	1600 500	46 14	80	68	2.5	1.5
24 Months of Exposure (All values were included in statistical analysis)										
100 ppm	20	25600 41800	8200 12300	46 17	3000 2400	28 15	900	4284	11.5	8.4
33 ppm	20	11800 13200	5100 3200	52 12	2500 1500	31 13	500	5400	8.0	4.2
10 ppm	18	12500 23400	3400-,a 1400	46 13	2400 1200	36 14	465	302	8.0	5.4
0 ppm (CI)	20	13400 21400	3900 2200	49 16	2200 600	31 11	600	254	9.5	4.2
0 ppm (CII)	18	13000 12700	6000 3900	54 16	2200 1200	26 13	755	771	8.5	4.8
24 Months of Exposure (Values from animals with leukemia were removed from statistical analysis)										
100 ppm	14	12900 19200	7900 14400	54 9	3000 1400	33 11	735	289	10.0	2.8
33 ppm	16	7000 3600	4000 2200	56 9	2400 1200	35 9	395	130	6.5	3.1
10 ppm	13	6300 2000	3200-,a 900	52 7	2500 1200	39 9	430	148	7.0	2.5
0 ppm (CI)	18	7200 3800	3900 2300	53 7	2300 600	34 6	600	224	9.0	2.9
0 ppm (CII)	14	9100 5400	5600 3900	59 11	2500 1200	30 10	500	610	7.5	2.8

a = $0.05 > p > 0.01$ b = $0.01 > p > 0.001$ c = $p < 0.001$

First letter of superscript denotes degree of significance vs. Air Control I (CI); second letter denotes degree of significance vs. Air Control II (CII). Bracketed superscripts denote values significantly higher than those of control groups. No statistical comparisons were made for monocytes.

[1]All absolute values are reported as number of cells counted per mm^3. The remaining WBC differential values are presented in Table 24.

N = Number of samples analyzed.

Mean ($\bar{X}$) and standard deviation (SD) are expressed for white blood cells, neutrophils and lymphocytes.
Median (Q_2) and quartile deviation (QD) are expressed for all other monocytes.

Table 24

Summary Values[1] of WBC Differential

for Male Rats Exposed to Ethylene Oxide Vapor

Exposure Concentration	N	White Blood Cells ($/mm^3$)		Bands				Eosinophils				Basophils				Nucleated RBC[2]	
				Absolute		(%)		Absolute		(%)		Absolute		(%)			
		$\bar{X}$ +	SD	Q_2	QD	Q_2	QD	Q_2	QD	Q_2	QD	Q_2	QD	Q_2	QD	Q_2	QD
6 Months of Exposure																	
100 ppm	10	4300	500	0	0	0	0	50	34	1	1	0	0	0	0	0	11
33 ppm	10	3800[a,-]	500	0	0	0	0	40	21	1	1	0	0	0	0	0	0
10 ppm	10	3700[b,-]	800	0	0	0	0	35	46	1	1	0	0	0	0	0	0
0 ppm (CI)	10	4700	900	0	0	0	0	45	65	1	1	0	0	0	0	0	0
0 ppm (CII)	10	4400	900	0	0	0	0	70	26	2	1	0	0	0	0	0	0
12 Months of Exposure																	
100 ppm	10	3500	1000	0	0	0	0	45	26	1	1	0	0	0	0	0	0
33 ppm	10	3600	500	0	0	0	0	30	20	1	0	0	0	0	0	0	0
10 ppm	10	4100	1600	0	12	0	0	50	32	1	1	0	0	0	0	0	31
0 ppm (CI)	10	3900	1400	0	0	0	0	15	29	0	1	0	0	0	0	0	0
0 ppm (CII)	10	3500	1100	0	0	0	0	50	28	1	1	0	0	0	0	0	0
18 Months of Exposure																	
100 ppm	20	3000	800	0	0	0	0	35	41	1	1	0	0	0	0	0	0
33 ppm	20	3600	1000	0	0	0	0	35	41	1	1	0	0	0	0	0	0
10 ppm	20	3300	900	0	0	0	0	35	39	1	1	0	0	0	0	0	0
0 ppm (CI)	20	3900	900	0	0	0	0	30	59	1	1	0	0	0	0	0	0
0 ppm (CII)	20	3500	1400	0	0	0	0	10	35	0	1	0	0	0	0	0	0
24 Months of Exposure (All values were included in statistical analysis)																	
100 ppm	20	25600	41800	0	49	0	0	90	95	1	1	0	0	0	0	100	194
33 ppm	20	11800	13200	0	231	0	2	60	52	1	1	0	0	0	0	55	280
10 ppm	18	12500	23400	0	31	0	0	25	65	0	1	0	0	0	0	45	69
0 ppm (CI)	20	13400	21400	25	34	0	0	105	70	2	1	0	0	0	0	65	79
0 ppm (CII)	18	13000	12700	0	56	0	1	120	124	1	1	0	0	0	0	0	102
24 Months of Exposure (Values from animals with leukemia were removed from statistical analysis)																	
100 ppm	14	12900	19200	0	42	0	0	105	82	2	1	0	0	0	0	25	108
33 ppm	16	7000	3600	0	19	0	0	60	45	1	1	0	0	0	0	50	59
10 ppm	13	6100	2000	0	15	0	0	50	62	1	1	0	0	0	0	0	40
0 ppm (CI)	18	7200	3800	25	31	0	0	110	71	2	1	0	0	0	0	55	71
0 ppm (CII)	14	9100	5400	0	42	0	0	95	85	1	1	0	0	0	0	0	52

a = $0.05 > p > 0.01$ b = $0.01 > p > 0.001$

No statistical comparisons were made for bands, basophils and nucleated RBC.

[1]All absolute values are reported as number of cells counted per mm^3.

[2]Expressed as number of cells per 100 white blood cells

N = Number of samples analyzed.

Mean ($\bar{X}$) and standard deviation (SD) are expressed for white blood cells. Median (Q_2) and quartile deviation (QD) are expressed for all other parameters.

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Table 25

Summary Values[1] of WBC Differential

for Female Rats Exposed to Ethylene Oxide Vapor

Exposure Concentration	N	White Blood Cells ($/mm^3$) $\bar{X} \pm SD$			Neutrophils Absolute $\bar{X} \pm SD$			Neutrophils (%) $\bar{X} \pm SD$			Lymphocytes Absolute $\bar{X} \pm SD$			Lymphocytes (%) $\bar{X} \pm SD$			Monocytes Absolute Q_2	Monocytes Absolute QD	Monocytes (%) Q_2	Monocytes (%) QD
6 Months of Exposure																				
100 ppm	10	3700	700	800	300	22	5	2800	500		76	6		0	0		0.0	0.0		
33 ppm	10	3900	700	800	300	21	8	3000	600		78	8		0	16		0.0	0.5		
10 ppm	10	3600	600	600	200	16	4	3000	500		82	4		0	5		0.0	0.1		
0 ppm (CI)	10	3900	600	700	200	17	5	3200	600		81	5		0	26		0.0	0.6		
0 ppm (CII)	10	4500	1300	1000	500	21	7	3400	900		77	7		0	32		0.0	0.6		
12 Months of Exposure																				
100 ppm	10	2100	900	800	500	38	10	1200	400		61	10		5	10		0.5	0.5		
33 ppm	10	2100	500	800	400	35	9	1300	300		63	9		10	10		0.5	0.5		
10 ppm	10	2400	500	700	200	31	9	1600	500		67	8		5	18		0.5	0.8		
0 ppm (CI)	10	2400	600	800	400	34	8	1500	300		64	8		10	18		0.5	0.6		
0 ppm (CII)	10	2800	1000	1000	500	33	11	1700	700		65	11		30	43		1.5	1.0		
18 Months of Exposure																				
100 ppm	18	2500	1500	1300	1100	46	11	1100	400		49	10		40	51		2.0	2.0		
33 ppm	20	2800	2400	1200	1100	42	8	1500	1400		53	7		50	46		2.5	1.9		
10 ppm	18	2100	700	900	300	43	8	1100	400		53	9		30	44		1.5	1.8		
0 ppm (CI)	20	2200	700	1000	500	41	10	1200	300		55	10		30	40		2.0	1.9		
0 ppm (CII)	18	2200	500	900	400	40	9	1200	300		56	9		50	31		2.5	1.5		
24 Months of Exposure (All values were included in statistical analysis)																				
100 ppm	18	12600	15300	4100(a,-)	4800	39	13	2000	1000		34	22		330	5131		6.5	23.8		
33 ppm	19	6900	9700	3000	4000	46	12	1600	300		41	16		149	290		4.0	5.0		
10 ppm	20	6200	6200	2900	3300	45	10	2200	1700		46	14		120	132		4.0	2.4		
0 ppm (CI)	19	8200	21200	1600	1100	40	13	1600	500		48	16		110	60		3.0	1.5		
0 ppm (CII)	19	8900	18100	2100	1500	41	13	1900	900		45	16		130	110		3.0	2.0		
24 Months of Exposure (Values from animals with leukemia were removed from statistical analysis)																				
100 ppm	7	4100(a,-)	900	2100	700	50	8	1800	500		44	9		90	95		3.0	1.5		
33 ppm	11	3300	1100	1700	900	49	9	1500[-,a]	300		47	9		70	70		3.0	2.0		
10 ppm	15	5800	6000	2600	2700	45	11	2200	1900		46	14		100	100		3.0	1.5		
0 ppm (CI)	17	3100	1100	1400	800	43	10	1600	400		52	9		110	55		3.0	1.2		
0 ppm (CII)	16	4000	2500	1800	1400	44	8	1900	600		50	10		100	55		3.0	1.5		

a = $0.05 > p > 0.01$

First letter of superscript denotes degree of significance vs. Air Control I (CI); second letter denotes degree of significance vs. Air Control II (CII). Bracketed superscripts denote values significantly higher than those of control groups. No statistical comparisons were made for monocytes.

[1]All absolute values are reported as number of cells counted per mm^3. The remaining WBC differential values are presented in Table 26.

n: Number of samples analyzed.

Mean ($\bar{X}$) and standard deviation (SD) are expressed for white blood cells, neutrophils and lymphocytes.

Median (Q_2) and quartile deviation (QD) are expressed for monocytes.

Table 26

Summary Values[1] of WBC Differential for Female Rats Exposed to Ethylene Oxide Vapor

Exposure Concentration	n	White Blood Cells ($/mm^3$)		Bands				Eosinophils				Basophils				Nucleated RBC[2]	
				Absolute		(%)		Absolute		(%)		Absolute		(%)			
		$\bar{X}$ ± SD		Q_2	QD	Q_2	QD	Q_2	QD	Q_2	QD	Q_2	QD	Q_2	QD	Q_2	QD
6 Months of Exposure																	
100 ppm	10	3700	700	0	0	0.0	0	45	21	1	0	0	0	0.0	0	0	22
33 ppm	10	3960	700	0	0	0.0	0	40	25	1	1	0	0	0.0	0	0	16
10 ppm	10	3600	600	0	16	0.0	0	45	40	1	1	0	0	0.0	0	0	28
0 ppm (CI)	10	3900	600	0	0	0.0	0	55	45	2	1	0	0	0.0	0	0	11
0 ppm (CII)	10	4500	1300	0	0	0.0	0	35	50	1	1	0	0	0.0	0	0	0
12 Months of Exposure																	
100 ppm	10	2100	900	0	0	0	0	0	12	0	0	0	0	0	0	0	10
33 ppm	10	2100	500	0	0	0	0	20	16	1	1	0	0	0	0	10	20
10 ppm	10	2400	500	0	0	0	0	20	15	1	0	0	0	0	0	10	26
0 ppm (CI)	10	2400	600	0	0	0	0	35	31	2	1	0	0	0	0	0	15
0 ppm (CII)	10	2800	1000	0	0	0	0	25	21	1	1	0	0	0	0	20	40
18 Months of Exposure																	
100 ppm	18	2500	1500	0	12	0.0	1	20	25	1	1	0	0	0.0	0	0	15
33 ppm	20	2800	2400	15	19	1.0	0	25	19	1	0	0	0	0.0	0	0	20
10 ppm	18	2100	700	0	12	0.0	0	20	20	1	1	0	0	0.0	0	0	25
0 ppm (CI)	20	2200	700	0	0	0.0	0	25	18	1	1	0	0	0.0	0	0	15
0 ppm (CII)	18	2200	500	0	0	0.0	0	20	21	1	1	0	0	0.0	0	0	0
24 Months of Exposure (All values were included in statistical analysis)																	
100 ppm	18	12600	15300	35	208	1	2	45	55	1	1	0	0	0	0	110	1558
33 ppm	19	6900	9700	0	20	0	0	60	55	1	2	0	0	0	0	100	85
10 ppm	20	6200	6200	0	28	0	0	50	49	1	1	0	0	0	0	0	91
0 ppm (CI)	19	9200	21200	0	15	0	0	40	50	1	2	0	0	0	0	60	60
0 ppm (CII)	19	8900	18100	0	25	0	0	50	35	1	1	0	0	0	0	90	60
24 Months of Exposure (Values from animals with leukemia were removed from statistical analysis)																	
100 ppm	7	4100(a,-)	900	0	20	0	0	40	10	1	0	0	0	0	0	0	25
33 ppm	11	3300	1100	0	10	0	0	20	30	1	0	0	0	0	0	70	30
10 ppm	15	5800	6000	0	0	0	0	50	50	1	1	0	0	0	0	0	55
0 ppm (CI)	17	3100	1100	0	15	0	0	40	42	1	2	0	0	0	0	60	52
0 ppm (CII)	16	4000	2500	0	19	0	0	50	32	1	1	0	0	0	0	85	75

^{a} $p < 0.05$, $^{-}$ $p > 0.01$

First letter of superscript denotes degree of significance vs. Air Control I (CI); second letter denotes degree of significance vs. Air Control II (CII). Bracketed superscripts denote values significantly higher than those of control groups. No statistical comparisons were made for bands, basophils, and nucleated RBC.

[1] All absolute values are reported as number of cells counted per mm^3.
[2] Expressed as number of cells per 100 white blood cells

n = Number of samples analyzed.

Mean ($\bar{X}$) and standard deviation (SD) are expressed for white blood cells. Median (Q_2) and quartile deviation (QD) are expressed for all other parameters.

(WBC) was elevated (not statistically significant) in the 100 ppm group. In the animals without leukemia, this was because of one animal (#59115). This animal died shortly after the blood collection period. It did not have leukemia but did have other pathologic conditions that explain the elevated WBC count. When this value was removed from statistical analysis, the mean WBC count was similar to that of the two controls. Consequently, since there was only one abnormal value, it is believed there were no treatment-related effects noted for the hematologic results.

Females

There were no dose-related hematologic values indicative of a toxicologic effect at the 6-month sacrifice period. At the 12- and 18-month intervals, the only notable findings were that the hemoglobin level and the erythrocyte count of the 100 ppm group were slightly lower than the control values and in some cases were significantly different from those of one control. There was no similar pattern of histologic findings noted at the 12- and 18-month intervals that support this apparent treatment-related effect.

There were no results or trends indicative of a toxicologic effect at the 24-month interval when results were corrected for the confounding effect of mononuclear cell leukemia. The uncorrected values for the 100 ppm group were different, some statistically significant, for several parameters when compared to the corresponding values of the controls. These changes were all believed to be related to mononuclear cell leukemia and were as follows: elevated WBC, neutrophils, monocytes and bands and depressed RBC and hemoglobin.

Serum Clinical Chemistry

The serum clinical chemistry summary values of the four sacrifice intervals for each sex are presented in Tables 27 and 28 for the male rats and in Tables 29 and 30 for the females. The clinical chemistry values for individual animals are presented in Appendix VII, Tables A-50 through A-56 for male rats and Tables A-57 through A-63 for female rats. Caution should be taken in the evaluation of the toxicologic significance of the data at the 24-month sacrifice interval, since, for all groups, the range of values for most parameters was so great. This phenomenon may be related to an age factor or to a pathologic condition, e.g., leukemia. Associated with the later stages of leukemia is involvement of many organs. Changes in certain serum chemistry values may, therefore, be expected, but there was no elimination of values performed for these serum chemistry analyses as was done in the hematologic analyses, because no definite cause and effect relationship could be established.

Males

At the 6- and 12-month sacrifice period, there were no dose-related effects that were indicative of a toxicologic response. The only significant result noted at the 18-month interval was in alkaline phosphatase value of the 100 ppm

Table 27

Summary Values for Serum Clinical Chemistry Determinations
for Male Rats Exposed to Ethylene Oxide Vapor

Exposure Concentration	N	GGT[1] (U/L) Q_2	GGT[1] (U/L) QD	HBDH[2] (U/L) $\bar{X}$ ± SD		ALP[3] (U/L) $\bar{X}$ ± SD		CPK[4] (U/L) $\bar{X}$ ± SD		LDH[5] (U/L) $\bar{X}$ ± SD		AST[6] (U/L) $\bar{X}$ ± SD		ALT[7] (U/L) $\bar{X}$ ± SD		Hb[8] (mg/dL) $\bar{X}$ ± SD	
6 Months of Exposure																	
100 ppm	10	0	0.0	212	60	226	19	77	16	210	64	67	11	42	15	3	2
33 ppm	10	0	0.0	190	65	227	18	81	37	184	62	67	15	37	5	4	4
10 ppm	10	0	0.0	175	87	232	20	77	39	168	87	65	12	36	7	3	4
0 ppm (CI)	10	0	0.0	186	93	235	14	76	31	184	99	71	19	40	12	3	4
0 ppm (CII)	10	0	0.0	167	78	243	19	76	27	161	79	62	13	34	5	2	3
12 Months of Exposure																	
100 ppm	10	0	0.0	138	127	181	14	63	44	124	118	76	70	46	11	4	5
33 ppm	10	0	0.0	154	94	172	17	75	49	145	92	84	31	55	31	5	6
10 ppm	10	0	0.0	230	113	175	16	97	44	222	108	119(-,a)	53	88	58	16	18
0 ppm (CI)	10	0	0.0	131	78	171	15	67	49	120	78	125	136	51	14	5	5
0 ppm (CII)	10	0	0.0	145	127	171	14	71	47	131	115	78	12	48	11	9	10
18 Months of Exposure																	
100 ppm	20	0	0.0	73	32	179(b,-)	29	99	118	58	30	77	21	49	16	4	2
33 ppm	20	0	0.4	68	28	150	34	68	48	54	26	66	16	46	13	4	3
10 ppm	20	0	0.8	76	75	163	20	66	44	65	65	72	28	46	21	6	10
0 ppm (CI)	20	0	0.0	82	47	156	21	96	105	68	40	76	24	48	15	6	7
0 ppm (CII)	20	0	0.0	87	82	167	19	56	68	67	68	72	18	43	11	6	6
24 Months of Exposure																	
100 ppm	20	-*		-*		174(a,-)	71	-*		-*		97	106	37	26	10	10
33 ppm	20	-		-		166(a,-)	48	-		-		76	38	36(a,-)	14	13	9
10 ppm	20	-		-		153	39	-		-		131	298	48	58	13	13
0 ppm (CI)	20	-		-		137	28	-		-		62	26	27	8	13	7
0 ppm (CII)	20	-		-		150	36	-		-		78	57	30	12	15	8

* $0.05 > p > 0.01$

First letter of superscript denotes degree of significance vs. Air Control I (CI); second letter denotes degree of significance vs. Air Control II (CII). Bracketed superscripts denote values significantly higher than those of control groups. No statistical comparisons were made for GGT.

[1] gamma glutamyltransferase
[2] hydroxybutyric dehydrogenase
[3] alkaline phosphatase
[4] creatine phosphokinase
[5] lactic dehydrogenase
[6] aspartate aminotransferase
[7] alanine aminotransferase
[8] serum hemoglobin

N = number of samples analyzed for most parameters. In certain cases quantity was not sufficient for individual determination.

Median (Q_2) and quartile deviation (QD) are expressed for GGT. Mean ($\bar{X}$) and standard deviation (SD) are expressed for all other parameters.

*No determinations were made for this parameter.

Table 28
Summary Values of Serum Clinical Chemistry Determinations
for Male Rats Exposed to Ethylene Oxide Vapor

Exposure Concentrations	N	Calcium (mg/dL.) X̄ ± SD		Glucose (mg/dL.) X̄ ± SD		Urea Nitrogen (mg/dL.) X ± SD		Creatinine (mg/dL.) X ± SD		Cholines-terase (U/L.) X ± SD		Total Bilirubin (mg/dL.) Q_2	QD	Total Protein (g/dL.) X ± SD		Albumin (g/dL.) X ± SD	
6 Months of Exposure																	
100 ppm	10	10.6	0.7	130	11	20	1	0.5	0.1	720	64	0.05	0.05	6.6	0.2	4.0	0.1
33 ppm	10	10.9	0.2	137	13	22	2	0.6	0.1	720	46	0.10	0.12	6.5	0.3	3.9	0.1
10 ppm	10	10.8	0.3	136	11	22	2	0.5	0.1	720	42	0.05	0.06	6.5	0.3	3.9	0.1
0 ppm (CI)	10	10.8	0.3	138	10	20	3	0.5	0.1	698	39	0.05	0.11	6.5	0.2	3.9	0.1
0 ppm (CII)	10	10.8	0.2	134	11	21	2	0.5	0.1	698	42	0.05	0.15	6.5	0.2	3.9	0.1
12 Months of Exposure																	
100 ppm	10	11.2	0.2	146	13	19	2	0.3	0.1	646	122	0.15	0.12	6.8	0.3	4.2	0.1
33 ppm	10	11.2	0.4	145	12	20	2	0.4(-,a)	0.1	710	113	0.35	0.15	6.7	0.2	4.1	0.1
10 ppm	10	11.2	0.4	147	8	20	2	0.3	0.1	697	113	0.35	0.12	6.8	0.2	4.1	0.1
0 ppm (CI)	10	11.2	0.2	147	7	18	2	0.3	0.1	688	112	0.40	0.26	6.6	0.2	4.1	0.1
0 ppm (CII)	10	11.0	0.4	147	9	19	2	0.3	0.0	632	96	0.30	0.06	6.5	0.3	4.1	0.1
18 Months of Exposure																	
100 ppm	20	11.0	1.5	158	27	15	1	0.6	0.2	946	305	0.00	0.09	7.1	0.4	3.9	0.3
33 ppm	20	10.9	1.5	151	17	16	1	0.6	0.2	943	148	0.00	0.09	7.0	0.3	3.8	0.2
10 ppm	20	11.3	0.8	147	16	15	1	0.6	0.2	903	196	0.00	0.14	6.8	0.3	3.8	0.2
0 ppm (CI)	20	11.3	0.9	149	22	15	1	0.6	0.1	921	170	0.00	0.10	6.9	0.2	3.8	0.3
0 ppm (CII)	20	11.4	0.8	149	14	15	1	0.5	0.2	904	112	0.00	0.05	6.8	0.3	3.7	0.2
24 Months of Exposure																	
100 ppm	20		-*		-*	26	8		-*		-*		-*		-*		-*
33 ppm	20		-		-	23	6		-		-		-		-		-
10 ppm	20		-		-	25	11		-		-		-		-		-
0 ppm (CI)	20		-		-	28	16		-		-		-		-		-
0 ppm (CII)	20		-		-	26	8		-		-		-		-		-

a = 0.05 > p > 0.01

First letter of superscript denotes degree of significance vs. Air Control I (CI); second letter denotes degree of significance vs. Air Control II (CII). Bracketed superscripts denote values significantly higher than those of control groups. No statistical comparisons were made for total bilirubin.

N = Number of samples analyzed for most parameters. In certain cases quantity was not sufficient for individual determination.

Median (Q_2) and quartile deviation (QD) are expressed for total bilirubin. Mean ($\bar{X}$) and standard deviation (SD) are expressed for all other parameters.

*No determinations were made for this parameter.

Table 29

Summary Values of Serum Clinical Chemistry Determinations for Female Rats Exposed to Ethylene Oxide Vapor

Exposure Concentrations	N	GGT[1] (U/L) Q_2	GGT[1] (U/L) QD	HBDH[2] (U/L) $\bar{X}$ ± SD	ALP[3] (U/L) $\bar{X}$ ± SD	CPK[4] (U/L) $\bar{X}$ ± SD	LDH[5] (U/L) $\bar{X}$ ± SD	AST[6] (U/L) $\bar{X}$ ± SD	ALT[7] (U/L) $\bar{X}$ ± SD	Hb[8] (mg/dL) $\bar{X}$ ± SD
6 Months of Exposure										
100 ppm	10	0.0	0.6	233 ± 74	244 ± 33	96 ± 36	211 ± 72	87(a,c) ± 16	47(-,b) ± 12	6 ± 6
33 ppm	10	0.5	0.6	211 ± 81	230 ± 15	91 ± 36	191 ± 70	79 ± 24	44 ± 16	5 ± 5
10 ppm	10	1.0	0.6	232 ± 68	233 ± 23	93 ± 26	210 ± 57	85(-,a) ± 23	44(-,a) ± 15	5 ± 5
0 ppm (CI)	10	1.0	0.6	211 ± 89	235 ± 25	111 ± 55	193 ± 84	70 ± 12	39 ± 9	2 ± 2
0 ppm (CII)	10	0.0	0.6	184 ± 90	233 ± 33	99 ± 69	169 ± 86	65 ± 8	33 ± 4	5 ± 7
12 Months of Exposure										
100 ppm	10	0.0	1.1	69 ± 30	157 ± 16	42 ± 20	60 ± 31	81 ± 31	47 ± 21	6 ± 9
33 ppm	10	1.0	1.1	60 ± 19	161 ± 26	47 ± 46	54 ± 18	83 ± 25	52 ± 18	5 ± 2
10 ppm	10	0.0	1.0	55 ± 24	156 ± 21	41 ± 20	48 ± 17	71 ± 17	45 ± 13	5 ± 3
0 ppm (CI)	10	0.0	0.1	65 ± 37	166 ± 16	45 ± 33	55 ± 30	77 ± 20	44 ± 10	5 ± 5
0 ppm (CII)	10	0.0	0.5	68 ± 42	164 ± 17	51 ± 30	55 ± 30	80 ± 27	49 ± 15	5 ± 4
18 Months of Exposure										
100 ppm	20	0.5	1.5	104 ± 99	169 ± 32	90 ± 79	104 ± 119	91(a,-) ± 56	52 ± 33	7 ± 7
33 ppm	20	2.0	1.5	81 ± 34	172 ± 31	92 ± 79	74 ± 34	82(a,-) ± 36	51 ± 21	6 ± 5
10 ppm	20	0.0	1.0	86 ± 64	167 ± 24	156 ± 302	78 ± 65	73 ± 24	43 ± 11	6 ± 5
0 ppm (CI)	20	0.0	0.9	65 ± 29	158 ± 32	65 ± 42	59 ± 26	63 ± 17	40 ± 12	4 ± 2
0 ppm (CII)	20	0.0	1.5	88 ± 69	171 ± 24	166 ± 294	83 ± 72	74 ± 31	44 ± 14	8 ± 11
24 Months of Exposure										
100 ppm	20	-*		-*	238(b,b) ± 83	-*	-*	218(a,a) ± 183	73(a,-) ± 38	10 ± 7
33 ppm	20	-		-	172 ± 36	-	-	123 ± 114	52 ± 26	10 ± 6
10 ppm	20	-		-	180 ± 54	-	-	104 ± 70	51 ± 27	10 ± 6
0 ppm (CI)	20	-		-	160 ± 36	-	-	107 ± 89	48 ± 18	12 ± 8
0 ppm (CII)	20	-		-	169 ± 55	-	-	107 ± 130	50 ± 38	16 ± 13

a = $0.05 > p > 0.01$ b = $0.01 > p > 0.001$ c = $p < 0.001$

First letter of superscript denotes degree of significance vs. Air Control I (CI); second letter denotes degree of significance vs. Air Control II (CII). Bracketed superscripts denote values significantly higher than those of control groups. No statistical comparisons were made for GGT.

[1]gamma glutamyltransferase
[2]hydroxybutyric dehydrogenase
[3]alkaline phosphatase
[4]creatine phosphokinase
[5]lactic dehydrogenase
[6]aspartate aminotransferase
[7]alanine aminotransferase
[8]serum hemoglobin

N = Number of samples analyzed for most parameters. In certain cases quantity was not sufficient for individual determination.

Median (Q_2) and quartile deviation (QD) are expressed for GGT. Mean ($\bar{X}$) and standard deviation (SD) are expressed for all other parameters.

*No determinations were made for this parameter.

Table 30

Summary Values of Serum Clinical Chemistry Determinations for Female Rats Exposed to Ethylene Oxide Vapor

Exposure Concentrations	N	Calcium (mg/dL) $\bar{X} \pm SD$		Glucose mg/dL) $\bar{X} \pm SD$		Urea Nitrogen (mg/dL) $\bar{X} \pm SD$		Creatinine (mg/dL) $\bar{X} \pm SD$		Cholinesterase (U/L) $\bar{X} \pm SD$		Total Bilirubin (mg/dL) Q_2	QD	Total Protein (g/dL) $\bar{X} \pm SD$		Albumin (g/dL) $\bar{X} \pm SD$	
6 Months of Exposure																	
100 ppm	10	10.7	0.4	114	10	22	2	0.4	0.1	3348	495	0.10	0.05	6.7	0.3	4.2	0.2
33 ppm	10	10.8	0.5	113	13	22	2	0.4	0.1	3211	257	0.10	0.10	6.9	0.3	4.3	0.2
10 ppm	10	10.8	0.3	115	12	22	3	0.4	0.1	3180	383	0.05	0.05	6.8	0.3	4.2	0.2
0 ppm (CF)	10	10.8	0.2	121	12	22	3	0.5	0.1	3105	278	0.00	0.05	6.8	0.3	4.2	0.1
0 ppm (CH)	10	10.7	0.3	125	12	21	2	0.4	0.1	3114	403	0.05	0.06	6.9	0.3	4.3	0.2
12 Months of Exposure																	
100 ppm	10	10.4	0.4	140	10	22	3	0.4	0.1	3257	420	0.00	0.10	6.9	0.3	4.2	0.3
33 ppm	10	10.5	0.2	136	8	21	3	0.4	0.1	3170	479	0.00	0.08	7.0	0.2	4.4	0.3
10 ppm	10	10.4	0.3	132	14	21	3	0.4	0.1	3177	441	0.10	0.06	6.8	0.2	4.2	0.3
0 ppm (CF)	10	10.5	0.4	136	11	21	4	0.5	0.1	3083	666	0.10	0.15	6.9	0.5	4.3	0.2
0 ppm (CH)	10	10.6	0.3	127	17	22	3	0.4	0.1	3160	357	0.05	0.15	7.0	0.4	4.3	0.3
18 Months of Exposure																	
100 ppm	20	10.8	0.6	140	18	15	1	0.4	0.2	2770	674	0.00	0.18	7.0	0.5	4.1	0.3
33 ppm	20	10.7	1.0	136	12	15	1	0.4	0.1	2893	428	0.05	0.14	7.3	0.4	4.2	0.2
10 ppm	20	10.8	1.0	141	12	15	1	0.5	0.1	2881	413	0.10	0.09	7.2	0.4	4.2	0.2
0 ppm (CF)	20	10.7	1.0	136	13	15	1	0.5	0.1	2798	397	0.10	0.05	7.2	0.5	4.2	0.2
0 ppm (CH)	20	10.9	0.8	136	16	15	1	0.5	0.1	2865	486	0.10	0.15	7.2	0.4	4.2	0.2
24 Months of Exposure																	
100 ppm	20	-	-*	-	-*	16	3	-	-*	-	-*	-	-*	-	-*	-	-*
33 ppm	20	-	-	-	-	16	3	-	-	-	-	-	-	-	-	-	-
10 ppm	20	-	-	-	-	16	2	-	-	-	-	-	-	-	-	-	-
0 ppm (CF)	20	-	-	-	-	16	1	-	-	-	-	-	-	-	-	-	-
0 ppm (CH)	20	-	-	-	-	15	2	-	-	-	-	-	-	-	-	-	-

N = Number of samples analyzed

Median (Q_2) and quartile deviation (QD) are expressed for total bilirubin. Mean ($\bar{X}$) and standard deviation (SD) are expressed for all other parameters. No statistical comparisons were made for total bilirubin.

*No determinations were made for this parameter.

group. The mean of this group was numerically higher than the mean values for either control group and was significantly different from that one of the control groups. Similar results for alkaline phosphatase were noted at the 24-month interval. However, at this interval, not only the 100 ppm but also the 33 ppm group was numerically greater than both controls and statistically different from one. The toxicologic significance of these findings is unknown. The other serum chemistry results did not indicate a dose-response relationship and were not indicative of a toxicologic response.

Females

Some significant differences in the EO-treated groups were noted for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) at the 6-, 18- and 24-month intervals. For all significant differences, the mean value of the EO-treated group(s) was greater than the control value. A questionable toxicologic significance was placed on the statistically significant differences observed at 6 months because there was no definite dose-response relationship, and there was no histopathologic evidence to support the findings. Furthermore, these differences were not observed at the following analysis interval.

At the 18- and 24-month intervals, more of a dose-response relationship for AST was noted in the 100 and 33 ppm groups; however, it was not until the 24-month interval that the mean AST value for the 100 ppm group was outside the range of normal values and was significantly different from that of both control groups. At this same time period, the ALT and alkaline phosphatase mean values of the 100 ppm group were significantly different from those of one or both control groups.

Cytogenetic Studies

No treatment-related effects in chromosomal aberrations were observed in bone marrow cells of rats exposed to ethylene oxide for one year. No statistically significant differences were obtained for the "percentage of abnormal cells," the "average number of chromosomal aberrations per cell," or the "total number of chromosomal aberrations (per rat)" for either males or females exposed to 100 ppm of ethylene oxide when compared to values obtained for the air-control groups. The detailed results and conclusions of the cytogenetic study on chromosomal aberrations are presented in Appendix IV.

Technical problems were encountered (1) in the development of a successful procedure to culture rat leukocytes and (2) at the 6-month sacrifice interval in the preparation of acceptable chromosome spreads. Completion of both of these studies as outlined in the original protocol was not possible. Chromosomal preparations from rats at the 18-month sacrifice interval were saved for possible future evaluation, but initial examination indicated the presence of low numbers of mitotic cells. These slides, prepared at the request of the EO Steering Committee, were not included as part of the original study protocol.

Organ Weight and Body Weight at Sacrifice

Prior to each sacrifice, body weights were obtained on the non-fasted animals. Organ weights were expressed as absolute values and as percentages of these body weights (hereafter called relative values). The summary of relative values at the 6-, 12- and 18-month sacrifice intervals are presented in Tables 31 and 32 for male and female rats, respectively. Absolute values are presented in Tables 33 and 34. The individual animal values for all groups at each sacrifice interval are reported in Appendix VIII, Tables A-64 through A-67 for male rats and Tables A-68 through A-71 for female rats. No statistical analyses were made at the 24-month sacrifice, since many of the rats had one or more types of tumor that could directly affect the true organ or body weight, or indirectly affect the weight of organs as the result of hormonal change. Statistical significance at 6-, 12- and 18-month sacrifice intervals are presented in the tables for both relative and absolute organ weights. However, in this section, only relative organ weight values are discussed except where discussion of the absolute values adds more to the interpretation of the results.

Males

There were no significant differences noted for body weight values of the male rats sacrificed at 6, 12 or 18 months. There were isolated incidences of statistically significant differences in relative organ weight noted at each interval; however, none of these significant differences were supported by histologic or clinical chemistry findings. Furthermore, no effects that were noted at the 6-or 12-month intervals were observed at the following analysis interval; nor were significant differences between test and control group noted for the same organ weight for both sexes at the same interval. The means of the absolute brain weight at the 18-month interval were similar for all groups; therefore, since brain weights generally do not vary appreciably with change in body weights, the statistically significant relative brain weight was probably more a reflection of the difference in body weights than a treatment-related effect on the brain. Furthermore, there was no histologic evidence to support this finding. All other significant differences noted were not related to dose and are not considered to be of any toxicologic significance.

Concomitant with the increase in malignant mononuclear cells in the spleens of animals with leukemia at the 24-month sacrifice interval was an increase in spleen weights. There was no increase in the mean absolute or relative spleen weights at the 18-month interval in the EO-treated rats, which supports the histologic evaluation of there being no incidence of leukemia at the 18-month sacrifice interval for male rats.

Females

At each sacrifice interval, the mean body weight values of the sacrificed female rats were depressed, some slightly and some markedly, for the 100 and 33 ppm groups when compared to the control values. For each interval, the mean value of the 10 ppm group was similar to those of the controls.

Table 31

Summary Values of Organ Weights Expressed as Percentage of Body Weight for Male Rats Exposed to Ethylene Oxide Vapor

Exposure Concentration	N	Body Weight[1] $\bar{X} \pm$ SD		Organ Weight as Percentage of Body Weight: Liver $\bar{X} \pm$ SD		Kidneys $\bar{X} \pm$ SD		Spleen $\bar{X} \pm$ SD		Adrenals $\bar{X} \pm$ SD		Brain $\bar{X} \pm$ SD		Rt. Testicle $\bar{X} \pm$ SD		Lt. Testicle $\bar{X} \pm$ SD	
6 Months of Exposure																	
100 ppm	10	357	25	3.04(-,a)	0.09	0.672	0.034	0.162	0.006	0.013	0.001	0.541	0.031	0.403	0.030	0.412	0.014
33 ppm	10	360	26	2.95(b,c)	0.13	0.642	0.031	0.163	0.006	0.013	0.002	0.549	0.035	0.392	0.024	0.409	0.029
10 ppm	10	362	32	3.05	0.11	0.655	0.031	0.164	0.010	0.014	0.002	0.551	0.037	0.403	0.023	0.421	0.019
0 ppm (CI)	10	370	27	3.14	0.03	0.657	0.015	0.166	0.010	0.012	0.001	0.520	0.046	0.389	0.021	0.406	0.021
0 ppm (CII)	10	356	12	3.17	0.12	0.668	0.020	0.162	0.009	0.013	0.002	0.545	0.030	0.388	0.031	0.406	0.027
12 Months of Exposure																	
100 ppm	10	393	36	3.02	0.11	0.671	0.054	0.158	0.030	0.011	0.002	0.510	0.024	0.367	0.042	0.390(a,-)	0.022
33 ppm	10	426	27	3.07	0.24	0.654	0.034	0.147	0.011	0.010	0.002	0.473	0.029	0.358	0.028	0.350	0.063
10 ppm	10	428	29	3.04	0.18	0.655	0.043	0.142	0.010	0.014	0.006	0.470	0.035	0.357	0.042	0.365	0.030
0 ppm (CI)	10	420	40	3.01	0.19	0.651	0.035	0.149	0.010	0.011	0.001	0.478	0.049	0.353(-,a	0.024	0.360(-,a	0.027
0 ppm (CII)	10	402	27	3.08	0.15	0.677	0.032	0.147	0.014	0.012	0.004	0.505	0.034	0.379(a,-)	0.016	0.387(a,-)	0.017
18 Months of Exposure																	
100 ppm	20	422	26	3.06	0.28	0.665	0.032	0.167	0.029	0.012	0.004	0.487(a,-)	0.044	0.364	0.068	0.375	0.050
33 ppm	20	445	33	3.24	0.40	0.648(-,b	0.047	0.170	0.029	0.010(a,-	0.003	0.466	0.057	0.345(a,a	0.055	0.416	0.095
0 ppm	20	431	36	3.07	0.29	0.654(-,a	0.060	0.168	0.030	0.011(a,-	0.003	0.470	0.023	0.378	0.168	0.375	0.092
0 ppm (CI)	20	447	25	3.04	0.32	0.675	0.038	0.172	0.024	0.013	0.003	0.459	0.028	0.361	0.051	0.416	0.126
0 ppm (CII)	20	434	27	3.14	0.15	0.692	0.048	0.173	0.019	0.012	0.000	0.470	0.025	0.389	0.056	0.412	0.126

a - $0.05 > p > 0.01$ b - $0.01 > p > 0.001$ c - $p < 0.001$

First letter of superscript denotes degree of significance vs. Air Control I (CI); second letter denotes degree of significance vs. Air Control II (CII). Bracketed superscripts denote values significantly higher than those of control groups. No statistical comparisons were made for the 24 month sacrifice interval.

N - Number of samples analyzed

Mean ($\bar{X}$) and standard deviation (SD) are expressed for each parameter.

[1]Body weight is expressed in grams.

Table 32
Summary Values of Organ Weights Expressed as Percentage of Body Weight
for Female Rats Exposed to Ethylene Oxide Vapor

[illegible] Concentration	N	Body Weight[1] $\bar{X}$ ± SD		Organ Weight as Percentage of Body Weights: Liver $\bar{X}$ ± SD		Kidneys $\bar{X}$ ± SD		Spleen $\bar{X}$ ± SD		Adrenals $\bar{X}$ ± SD		Brain $\bar{X}$ ± SD	
6 Months of Exposure													
[illegible] ppm	10	$190^{c,a}$	7	3.16	0.50	0.716	0.033	0.194	0.014	0.025	0.003	0.920	0.046
33 ppm	10	$198^{b,-}$	13	3.16	0.43	0.714	0.036	0.198	0.016	0.024	0.003	0.884	0.098
10 ppm	10	$204^{a,-}$	11	3.18	0.48	0.709	0.027	0.187	0.015	0.024	0.003	0.886	0.045
0 ppm (CI)	10	$215^{(-,a)}$	10	3.14	0.43	0.697	0.038	0.192	0.011	0.023	0.003	0.848	0.051
0 ppm (CII)	10	$202^{a,-}$	14	3.14	0.47	0.733	0.028	0.197	0.015	0.025	0.003	0.885	0.052
12 Months of Exposure													
100 ppm	10	216	13	3.32	0.44	0.750	0.045	0.173	0.112	0.026	0.005	0.835	0.052
33 ppm	10	219	15	3.16	0.26	0.712	0.058	0.169	0.112	0.025	0.007	0.843	0.064
10 ppm	10	226	14	$2.99^{-,b}$	0.21	0.727	0.046	0.174	0.096	0.064	0.127	0.823	0.066
0 ppm (CI)	10	231	12	3.16	0.19	0.735	0.029	0.174	0.102	0.026	0.005	0.818	0.045
0 ppm (CII)	10	222	14	3.22	0.08	0.757	0.052	0.172	0.108	0.025	0.004	0.835	0.070
18 Months of Exposure													
100 ppm	20	$239^{c,c}$	18	$3.18^{(a,-)}$	0.36	0.707	0.038	0.224	0.168	0.021	0.004	$0.758^{(b,b)}$	0.072
33 ppm	20	$255^{-,a}$	15	2.95	0.16	0.668	0.047	0.166	0.023	0.018*	0.176	0.730	0.045
10 ppm	20	264	14	3.01	0.26	0.667	0.070	0.160	0.016	0.020	0.005	0.688	0.072
0 ppm (CI)	20	264	17	2.98	0.21	0.665	0.041	0.166	0.022	0.019*	0.008	0.705	0.047
0 ppm (CII)	20	269	16	2.99	0.23	0.676	0.046	0.156	0.015	0.018	0.005	0.700	0.055

a = $0.05 > p > 0.01$ b = $0.01 > p > 0.001$ c = $p < 0.001$

First letter of superscript denotes degree of significance vs. Air Control I (CI); second letter denotes degree of significance vs. Air Control II (CII). Bracketed superscripts denote values significantly higher than those of control groups. No statistical comparisons were made for the 24-month sacrifice interval.

N = Number of samples analyzed

*N = 18 for 33 ppm group, 19 for CI

Mean ($\bar{X}$) and standard deviation (SD) are expressed for each parameter.

[1]Body weight is expressed in grams

WPC/1043

Table 33

Summary of Absolute Organ Weights for Male Rats Exposed to Ethylene Oxide Vapor

Exposure Concentration	N	Absolute Organ Weights													
		Body Weight[1]		Liver		Kidneys		Spleen		Adrenals		Brain		Rt. Testicle		Lt. Testicle	
		$\bar{X}$	± SD	$\bar{X}$	± SD	$\bar{X}$	± SD	$\bar{X}$	± SD	$\bar{X}$	± SD	$\bar{X}$	± SD	$\bar{X}$	± SD	$\bar{X}$	± SD
6 Months of Exposure															
100 ppm	10	357	25	10.85	0.75	2.40	0.24	0.58	0.05	0.045	0.004	1.93	0.08	1.44	0.11	1.47	0.08
33 ppm	10	360	26	10.60	0.79	2.31	0.18	0.59	0.04	0.046	0.007	1.97	0.07	1.41	0.13	1.47	0.13
10 ppm	10	362	32	11.06	1.21	2.37	0.25	0.59	0.05	0.051	0.006	1.98	0.08	1.45	0.10	1.52	0.10
0 ppm (CI)	10	370	27	11.65	1.35	2.43	0.14	0.61	0.05	0.045	0.004	1.91	0.08	1.44	0.05	1.50	0.05
0 ppm (CII)	10	356	12	11.28	0.72	2.37	0.04	0.58	0.04	0.047	0.005	1.94	0.06	1.38	0.08	1.44	0.07
12 Months of Exposure															
100 ppm	10	393	36	11.88	1.41	2.63	0.22	0.62	0.11	0.045	0.008	2.00	0.10	1.44	0.21	1.53	0.12
33 ppm	10	426	22	13.06	0.97	2.78	0.12	0.63	0.04	0.044	0.006	2.01	0.07	1.52	0.13	1.48	0.25
10 ppm	10	428	29	13.02	1.22	2.80	0.27	0.61	0.04	0.058	0.026	2.01	0.08	1.53	0.17	1.56	0.09
0 ppm (CI)	10	420	40	12.64	1.44	2.73	0.21	0.63	0.06	0.046	0.005	1.99	0.10	1.47	0.10	1.51	0.13
0 ppm (CII)	10	402	27	12.34	0.95	2.72	0.23	0.59	0.08	0.047	0.014	2.02	0.10	1.52	0.12	1.56	0.12
18 Months of Exposure															
100 ppm	20	422	26	12.93	1.48	$2.80^{b,a}$	0.19	0.70	0.12	0.053	0.016	2.05	0.10	$1.53^{a,-}$	0.28	$1.58^{-,a}$	0.22
33 ppm	20	445	33	14.41	2.08	2.88	0.26	0.76	0.15	$0.046^{b,-}$	0.011	2.06	0.17	1.53	0.26	1.83	0.31
10 ppm	20	431	36	13.20	1.12	$2.81^{a,a}$	0.21	0.72	0.11	$0.046^{b,-}$	0.013	2.02	0.11	1.62	0.67	1.61	0.42
0 ppm (CI)	20	447	25	13.58	1.27	3.01	0.17	0.77	0.11	0.060	0.015	2.05	0.09	1.70	0.25	1.86	0.56
0 ppm (CII)	20	434	27	13.61	1.17	3.00	0.30	0.75	0.09	0.052	0.012	2.04	0.10	1.69	0.31	1.87	0.53

a = $0.05 > p > 0.01$ b = $0.01 > p > 0.001$

First letter of superscript denotes degree of significance vs. Air Control I (CI); second letter denotes degree of significance vs. Air Control II (CII). No statistical comparisons were made for the 24-month sacrifice interval.

N = Number of samples analyzed

Mean ($\bar{X}$) and standard deviation (SD) are expressed for each parameter.

[1]Body weight is expressed in grams

Table 34

Summary of Absolute Organ Weights for Female Rats Exposed to Ethylene Oxide Vapor

Exposure Concentration	N	Body Weight[1] $\bar{X} \pm$ SD		Absolute Organ Weights: Liver $\bar{X} \pm$ SD		Kidneys $\bar{X} \pm$ SD		Spleen $\bar{X} \pm$ SD		Adrenals $\bar{X} \pm$ SD		Brain $\bar{X} \pm$ SD	
6 Months of Exposure													
100 ppm	10	190^{c,a}	7	6.01	0.62	1.36^{b,b}	0.09	0.37	0.03	0.048	0.006	1.75	0.07
33 ppm	10	198$^{b,-}$	13	6.26	0.43	1.42	0.08	0.39	0.04	0.048	0.006	1.75	0.21
10 ppm	10	204$^{a,-}$	11	6.49	0.65	1.45	0.10	0.38	0.03	0.048	0.006	1.81	0.08
0 ppm (CI)	10	215$^{(-,a)}$	10	6.75	0.43	1.50	0.10	0.41	0.03	0.049	0.008	1.82	0.11
0 ppm (CII)	10	202$^{a,-}$	14	6.36	0.66	1.48	0.08	0.40	0.03	0.050	0.005	1.79	0.09
12 Months of Exposure													
100 ppm	10	216	13	7.16	1.00	1.62	0.13	0.37	0.03	0.056	0.011	1.80	0.07
33 ppm	10	219	15	6.93	0.69	1.56	0.16	0.37	0.03	0.054	0.012	1.84	0.05
10 ppm	10	226	14	6.77	0.71	1.64	0.11	0.39	0.03	0.144	0.281	1.86	0.05
0 ppm (CI)	10	231	12	7.31	0.71	1.70	0.10	0.40	0.03	0.060	0.012	1.88	0.06
0 ppm (CII)	10	222	14	7.17	0.52	1.68	0.17	0.38	0.02	0.056	0.009	1.85	0.08
18 Months of Exposure													
100 ppm	20	239^{c,c}	18	7.62	1.05	1.67$^{-,b}$	0.12	0.54	0.41	0.049	0.007	1.80	0.11
33 ppm	20	255$^{-,a}$	15	7.52	0.67	1.70$^{-,a}$	0.12	0.42	0.05	0.046*	0.008	1.86	0.10
10 ppm	20	264	14	7.94	0.80	1.75	0.16	0.42	0.05	0.053	0.012	1.81	0.15
0 ppm (CI)	20	264	17	7.87	0.68	1.75	0.12	0.44	0.06	0.049*	0.010	1.85	0.09
0 ppm (CII)	20	269	16	8.11	0.79	1.82	0.15	0.42	0.04	0.047	0.012	1.88	0.09

a = $0.05 > p > 0.01$ b = $0.01 > p > 0.001$ c = $p < 0.001$

First letter of superscript denotes degree of significance vs. Air Control I (CI); second letter denotes degree of significance vs. Air Control II (CII). Bracketed superscripts denote values significantly higher than those of control groups. No statistical comparisons were made for the 24-month sacrifice interval.

N = Number of samples analyzed

*N = 18 for 33 ppm group, 19 for CI

Mean ($\bar{X}$) and standard deviation (SD) are expressed for each parameter.

[1]Body weight is expressed in grams

WPC/1105A

After 6 or 12 months of exposure, there were no significant treatment-related effects observed for the relative organ weight values. At the 18-month interval, all relative organ weights for the 100 ppm group were increased, and some were significantly different when compared to the controls. The higher organ to body weight ratios may have been primarily the result of relatively more body weight than organ weight depression at this period.

At the 18-month sacrifice interval, only one female rat was histologically confirmed to have leukemia. When this value (from the 100 ppm group) was removed from statistical analysis, along with another value of an animal (100 ppm group) with extramedullary hematopoiesis in the spleen, there was no indication of differences in spleen weights between EO-exposed and control groups. Both a statistically significant increase in relative liver weights and in AST serum chemistry values were noted in the 100 ppm group at the 18-month interval. However, no toxicologic significance was given to these findings because the increase in organ weights was not correlated (correlation coefficient for the 20 rats sacrificed at this period was not significant, $r = -0.272$) to the increase in AST values, nor was there histologic evidence to support a toxic effect. The mean value of the relative brain weight for the 100 ppm group was significantly increased in comparison to both controls; however, this is believed to be of no toxicologic importance for the same reason given under the section on organ weight for the males.

Gross Pathology

No biologically significant gross lesions which could be attributed to treatment were found at the 6-, 12- or 18-month sacrifice intervals. Only a few gross lesions were increased in frequency in treated animals at the final sacrifice interval. At this latter interval, there was an increase in enlarged adrenals in males exposed to 100 ppm of EO which were histologically confirmed to be pheochromocytomas in this group. Also, gross splenic abnormalities which were histologically confirmed to be mononuclear cell leukemia were present in males and females exposed to 100 ppm of EO. However, the increase in gross lung lesions in the females exposed to 100 ppm of EO for 24 months was associated with a variety of unrelated histologic findings and was probably not a result of treatment. Expected age-associated spontaneous gross lesions were seen in control and treated animals at each sacrifice interval. All gross findings are presented in more detail in the appropriate pathology reports contained in the Appendices.

Histopathology

Some treatment-related histologic changes were observed at the different sacrifice intervals during this study. All pathologic findings are presented in more detail in the appropriate pathology reports contained in the Appendices, of which this section is a summary.

Splenic Hemosiderosis: The only histologic change after 6 months of exposure which could be potentially treatment-related was an increase in splenic hemosiderosis in female rats exposed to 100 ppm of ethylene oxide. However, in the absence of anemia, bone marrow hyperplasia or enhanced spleen weights, this finding was considered to be not biologically significant. Furthermore, there was no increase in splenic hemosiderosis noted at the subsequent sacrifice intervals of 12, 18 or 24 months.

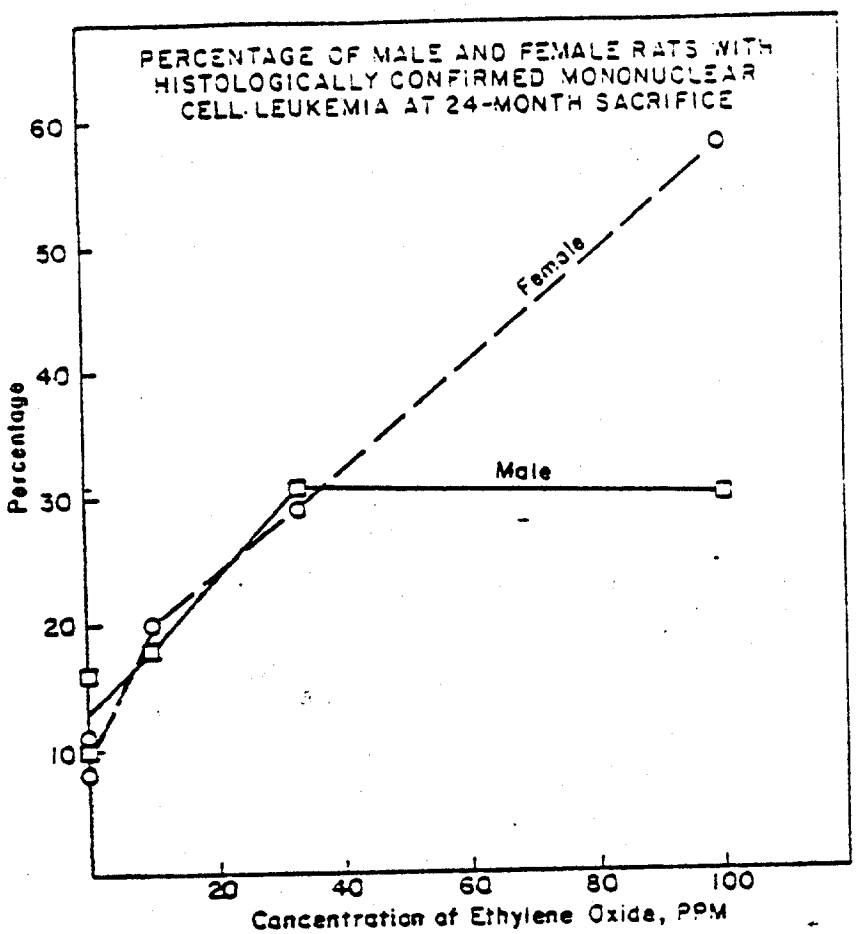
Focal Fatty Metamorphosis of the Adrenals: An elevated frequency of focal fatty metamorphosis of the adrenal cortices was first noted at 18 months in male rats exposed to 100 or to 33 ppm of ethylene oxide. After 24 months of exposure, this same lesion was significantly elevated in both sexes exposed to these same concentrations. The biological significance of focal fatty metamorphosis of the adrenal cortex is not known.

Subcutaneous Fibroma: There was an increased prevalence of histologically diagnosed fibroma in the subcutis of males in the 100 and 10 ppm groups after 24 months of exposure, statistically significant only at 100 ppm. Since the subcutis is diffusely spread over the body, sampling sites for microscopic examination were influenced by the gross observation of tumors and lesions in the skin and underlying subcutis. When a grossly evident tumor was observed in the skin or subcutis, a tissue sample for histologic assessment of subcutis was submitted from the tumor site in addition to the skin and subcutis from the flank region, which was routinely submitted for microscopic examination. Consequently, the sampling of the subcutis was influenced by the presence or absence of gross lesions obviating the documentation of lesions too small to be grossly detected. Considering the frequency of gross lesion in the skin and subcutis in assessing the significance of the microscopic prevalence data, and the absence of this finding in the 33 ppm males, it is concluded that the increased prevalence of subcutaneous fibromas in the 100 ppm males represents an effect of treatment, while the non-statistically significant increase in the 10 ppm males is a spurious finding unrelated to treatment.

Mononuclear Cell Leukemia: An enhanced prevalence of mononuclear cell leukemia was observed in the EO-treated animals at the 24-month sacrifice interval (See Appendix XII, pages 16 and 17 for pathologic features of this leukemia). More female rats were affected than the males. Statistical significance was observed in only the 100 ppm female group; however, the frequency for the females in the 33 and in the 10 ppm groups indicated a dose response (Figure 7-A). The prevalences for the female rats at this interval were 58, 29 and 20% for the 100, 33 and 10 ppm groups, respectively, whereas the prevalence for the control groups were 8 and 11%. Prevalences for male rats were 30, 31 and 18% for the 100, 33 and 10 ppm groups, respectively. The prevalences for the male control groups were 10 and 16%. In the males, one rat in the 100 ppm group and two rats in the 33 ppm group were determined to have mononuclear cell leukemia but did not have definitive splenic involvement. [Note: A more detailed statistical evaluation of this neoplasm is presented in the following section: "Frequency of Neoplasms that were Determined to be Potentially Treatment-Related".]

As noted in the "Routine Hematology with Leukocyte Differential Evaluation" section (page 42), there was substantial agreement between the hematologic and histologic evaluations confirming mononuclear cell leukemia. Furthermore, there was agreement between elevated relative spleen weights (expressed as a percentage of body weight) and histologic evaluation confirming leukemia. In both sexes, at each concentration level, including the controls, the mean relative spleen weight of the rats with leukemia was statistically significantly higher than the mean of the rats without leukemia; an average of five times higher in the males and approximately eight times higher in the females. However, there was little difference in relative spleen weights among the different concentration groups; i.e., in the rats with leukemia the means at 100 ppm, 33 ppm, 10 ppm, C-I and C-II were all similar.

Figure 7-A



Peritoneal Mesothelioma: At the 24-month sacrifice interval, low frequencies, between 2% and 4%, of mesothelioma of the peritoneum (listed under the testis in Table 2, Appendix XII) in male rats were observed in both air control groups and in the 10 ppm group. However, the frequency for the 100 ppm group was 13%, and that for the 33 ppm group was 10%. This enhanced prevalence in the 100 and 33 ppm groups is considered a treatment-related effect (See Appendix XII, page 16, for pathologic features of mesothelioma). It is noted that peritoneal mesothelioma was the principal histopathologic effect observed in the male rats that died spontaneously, or were euthanatized when moribund, in the 100 ppm group. [Note: A more detailed statistical evaluation of this neoplasm is presented in the following section: "Frequency of Neoplasms that were Determined to be Potentially Treatment-Related".]

Other Treatment-Related Effects: A significant increase in the frequency of atrophy (mild) of gastrocnemius muscle (not neurogenic) was noted in both sexes in only the 100 ppm group at the final sacrifice interval. As there were no gross lesions observed in this tissue at any of the scheduled sacrifice intervals, it was histologically examined only at the 6- and 24-month intervals. At the final sacrifice interval, there was a statistically significant bone marrow hyperplasia observed in female rats exposed to 100 ppm. This is believed to be a response to the anemic effects of mononuclear cell leukemia.

No other treatment-related effects were discerned from evaluation of the histologic data from the four scheduled sacrifice intervals or from animals that died spontaneously.

Frequency of Neoplasms That Were Determined to be Potentially Treatment-Related

The frequencies of certain tumor types of several organs were selected for further statistical analysis. This selection was based on whether significant differences in prevalence of the tumors were observed at one of the scheduled sacrifice intervals or if the proportion of all animals with the tumor, including the ones that died, appeared greater in the EO-exposed groups than in the controls.

Peto (1974) stated that a sharp distinction should be made between "incidental" tumors (discovered at the necropsy of a rat which died probably of something else) and "non-incidental" tumors (types of tumors that could or probably did cause death in the rat). Because different statistical methods are appropriate for analyzing the data from these two categories of tumors, tumors in this study were classified "incidental" or "non-incidental".

The following "non-incidental" tumors were statistically analyzed using a life table method of analysis: mononuclear cell leukemia (males); mononuclear cell leukemia (females); peritoneal mesotheliomia (males) and pituitary adenoma (males and females). This method of analysis takes into account all animals on the study, whether the animal died or was sacrificed at a scheduled interval or whether it was or was not (i.e., lost to follow-up) histologically examined. Pituitary adenoma was included in the statistical analyses of incidental and "non-incidental" tumor types because of its anatomical location.

For the types of tumors that were "incidentally" found either because the animal died or was sacrificed but the tumor was not the primary cause of death, the life table results are presented, but the statistical comparisons were made by a method described by Gart et al. (1979). The incidental tumors evaluated were the following: adrenal pheocromocytoma (males); pancreas islet cell adenoma (males); thyroid follicular adenoma (males); and testes interstitial cell tumor (males). [Note: Pituitary adenoma was also analyzed by this method.]

Additional statistical tests for positive trends were also used (Thomas et al., 1977; Gart et al., 1979). Time-adjusted trend test analyses were performed to compensate for bias associated with differential mortality in the various treatment groups. The adjusted analyses are sensitive not only to differences in relative tumor frequencies among groups but also to the time of observation of the tumors. Thus, the trend test indicates not only whether the treatment results in more tumors but also earlier tumors. Since some of the tumors in this study were detected at death, the assumption must be made that the tumor caused the death of the animal for these statistical trend tests to be valid. Furthermore, for the types of tumor compared, when they were found in rats sacrificed for examination, it was assumed that the rat "died" at that time because of the tumor. Therefore, the trend analysis was not applied to tumors which were only "incidental" findings at the death of the animals (Gart et al., 1979). The following tumor types of the EO-treated and control groups were compared using this statistical test for positive trend: mononuclear cell leukemia (males and females), peritoneal mesotheliomia (males), and pituitary adenoma (males and females).

A summary of the total number of "non-incidental" tumors for each group, along with the time before the development of the first tumor and the median time to tumor are presented in Table 35. Caution must be taken in evaluating all tumor frequency data, particularly for the incidental tumors. As before mentioned, Peto (1974) has stated that "death causes the necropsy of the dead

Table 35
Summary of Selected Tumor Incidence Comparisons for Male and Female Rats Exposed to Ethylene Oxide for Two Years

Concentration Ethylene Oxide, ppm	Total No. of Rats With Tissues Examined	Total No. of Rats With Tumor	Time, Months to First Tumor	Time, Months to Median Tumor[1]
Mononuclear Cell Leukemia - Males				
100	119	26	19	24
33*	81	25	13	25
10*	79	21	20	25
0-I	116	20	18	23
0-II	118	18	21	25
Mononuclear Cell Leukemia - Females				
100	113	28	18	24
33*	79	24	18	24
10*	77	14	19	25
0-I	118	9	19	24
0-II	117	13	18	23
Peritoneum Mesothelioma - Males				
100	119	22	15	23
33*	91	7	18	25
10*	89	3	20	-
0-I	114	2	18	-
0-II	116	2	20	-
Pituitary Adenoma - Males				
100	117	27	15	25
33*	79	16	15	25
10*	80	27	18	25
0-I	117	28	17	25
0-II	117	22	18	25
Pituitary Adenoma - Females				
100	117	32	10	24
33*	90	38	17	25
10*	90	39	16	24
0-I	119	38	15	25
0-II	116	38	18	25

*Only organs with gross lesions were histologically examined from this exposure level at the 6-, 12- and 18-month sacrifice intervals.

[1]Medians were not presented if the total number of particular tumor was 3 or less.

animals to occur, and, if an otherwise unsuspected tumor is discovered at necropsy, then the death of the animal caused the discovery of that tumor." Consequently, if some factor other than the presence of the tumor was involved in the cause of the animal's death, and if in one or more groups (e.g., 100 ppm and 33 ppm) there is significant increase in mortality, then the time to tumor, median time to tumor, and the statistical frequency analysis at different time periods other than at scheduled sacrifice periods are probably inaccurate.

Compiled in Appendix XIV, Tables A-72 through A-80 are the life table analysis data used in determining the cumulative proportions of rats developing the tumor for each "non-incidental" and "incidental" tumor types compared above. Presented in Figures 8 through 16 are graphs illustrating, for each of these tumors, the cumulative proportion of rats developing the tumor for each exposure month. Table 36 is a summary of the results from the life table analysis with the statistically significant differences indicated for each of the "non-incidental" tumor types.

Males, Mononuclear Cell Leukemia: (Table A-72 and Figure 8). Three rats with leukemia were observed in the 33 ppm group before the first observation of this tumor in the control or in the other EO-exposed groups.

The value of the cumulative percentage of males developing the tumor was higher in the 100 ppm group when compared to one or both control groups from the 23rd exposure month until and including the termination of the study. It was not until the 25th month that the value for the 33 ppm group was elevated (not statistically significant). The final cumulative percentages of the rats at risk developing this tumor were 61, 55 and 41% for the 100, 33 and 10 ppm groups, respectively, and 36 and 40% for the two control groups. The mortality-adjusted trend analysis resulted in a significant trend with respect to EO treatment ($p < 0.01$). This result indicates that exposure to ethylene oxide was associated with higher frequency and/or earlier observation of this leukemia in male rats.

Females, Mononuclear Cell Leukemia: (Table A-73 and Figure 9). The time to the first tumor was the 18th month for the 100 ppm, 33 ppm and Air Control II groups. From the 22nd month until the termination of the study, the value of the cumulative percentage developing the tumor in the 100 ppm group was numerically higher than the values of both controls and significantly different at the 24th and 25th exposure months. The value of the 33 ppm group was significantly higher than the values of one control and the values for the combined controls for the 24th and 25th months. At the termination of the study, the values of the cumulative percentage developing the tumor were 79, 50, 36, 21 and 28% for the 100 ppm, 33 ppm, 10 ppm, Air Control I and Air Control II groups, respectively. The prevalence of leukemia at the final sacrifice interval appeared to be related to dose at each exposure level (Figure 7-A). The regression analysis of final sacrifice tumor frequency vs. exposure concentration data was significant ($p < 0.01$), and the correlation coefficient (r) was +0.99 which indicates that the effect was highly correlated to the treatment at each exposure level. Furthermore, there was a significant positive

Table 36
Summary of "Non-Incidental" Tumor Prevalence
with Statistical Comparisons for Rats Exposed to Ethylene Oxide for Two Years

Exposure Month	Exposure Concentrations 100 ppm	33 ppm	10 ppm	0 ppm-I	0 ppm-II	Controls* 0-I & 0-II
Cumulative Percentage[1] of Rats with Mononuclear Cell Leukemia - Male						
13		1				
14		1				
15		2				
16		2				
17		3		2		1
18		3		2		1
19	1	3		4		2
20	3	5	3	6	3	5
21	6	8	4	11	3	7
22	6	11	5	15(-,b)	3b,-	9
23	18(-,a,-)	14	8	18	7	12
24	24	16	14	36	40	38
25	61	55	41	(116)	(118)	(234)
(N^2)	(119)	(81)	(79)			
Cumulative Percentage[1] of Rats with Mononuclear Cell Leukemia - Female						
18	1	1			1	1
19	1	4	1	1	1	1
20	3	6	1	1	4	3
21	5	7	1	1	6	3
22	11	7	1	1	6	3
23	13	10	4	4	10	7
24	44(c,b,c)	26(a,-,a)	12	8	14	10
25	79(c,c,c)	50(a,-,a)	36	21	28	24
(N^2)	(113)	(79)	(77)	(118)	(117)	(235)
Cumulative Percentage[1] of Rats with Peritoneal Mesothelioma - Male						
15	1					
16	1					
17	1			1		1
18	5	1		1		1
19	5	1	1	1	1	1
20	8	1	1	1	1	1
21	12(a,a,a)	1	1	1	1	1
22	12(a,a,a)	3	1	1	1	1
23	19(b,b,c)	3	1	1	1	1
24	23(c,c,c)	3	1	5	5	5
25	47(c,c,c)	22	8	(114)	(116)	(230)
(N^2)	(119)	(91)	(89)			

(Continued)

Table 36 (Continued)

Exposure Month	Exposure Concentrations 100 ppm	33 ppm	10 ppm	0 ppm-I	0 ppm-II	Controls* 0-I & 0-II
	Cumulative Percentage[1] of Rats with Pituitary Adenoma - Male					
15	2	1				
16	2	1				
17	2	1		1		1
18	8	1	1	6	4	5
19	8	1	1	6	4	5
20	9	1	2	7	4	5
21	11	1	4	7	5	6
22	11	3	8	8	5	7
23	13	3	8	10	6	8
24	17	3	11	13	6	10
25	64	48	55	56	47	51
(N^2)	(117)	(79)	(89)	(114)	(116)	(230)
	Cumulative Percentage[1] of Rats with Pituitary Adenoma - Female					
10	1					
11	1					
12	1					
13	2					
14	2					
15	3			1		1
16	4		1	1		1
17	4	1	2	1		1
18	10	7	7	2	1	2
19	11	8	11	2	3	2
20	13	8	11	4	9	6
21	16(a,-,-)	10	11	4	11	7
22	22(b,-,a)	11	11	4-,a	12(a,-)	8
23	24	16	17	9	15	12
24	42(a,-,a)	26	26	20	27	23
25	75	74	71	71	70	71
(N^2)	(117)	(90)	(90)	(119)	(116)	(235)

a = $0.05 > p > 0.01$ b = $0.01 > p > 0.001$ c = $p < 0.001$

First letter of superscript denotes degree of significance vs. Air Control I (0 ppm-I); second letter denotes degree of significance vs. Air Control II (0 ppm-II); third letter denotes degree of significance vs. combined control groups (0 ppm-I plus 0 ppm-II). Bracketed superscripts denote values significantly higher than those of control groups.

[1]Determined by Life Table Analysis

[2](N) = Tissues examined from this number of rats. Only gross lesions, not all tissues, were examined from the 33 and 10 ppm groups at 6, 12 and 18 months of exposure.

*Control groups combined

Figure 8

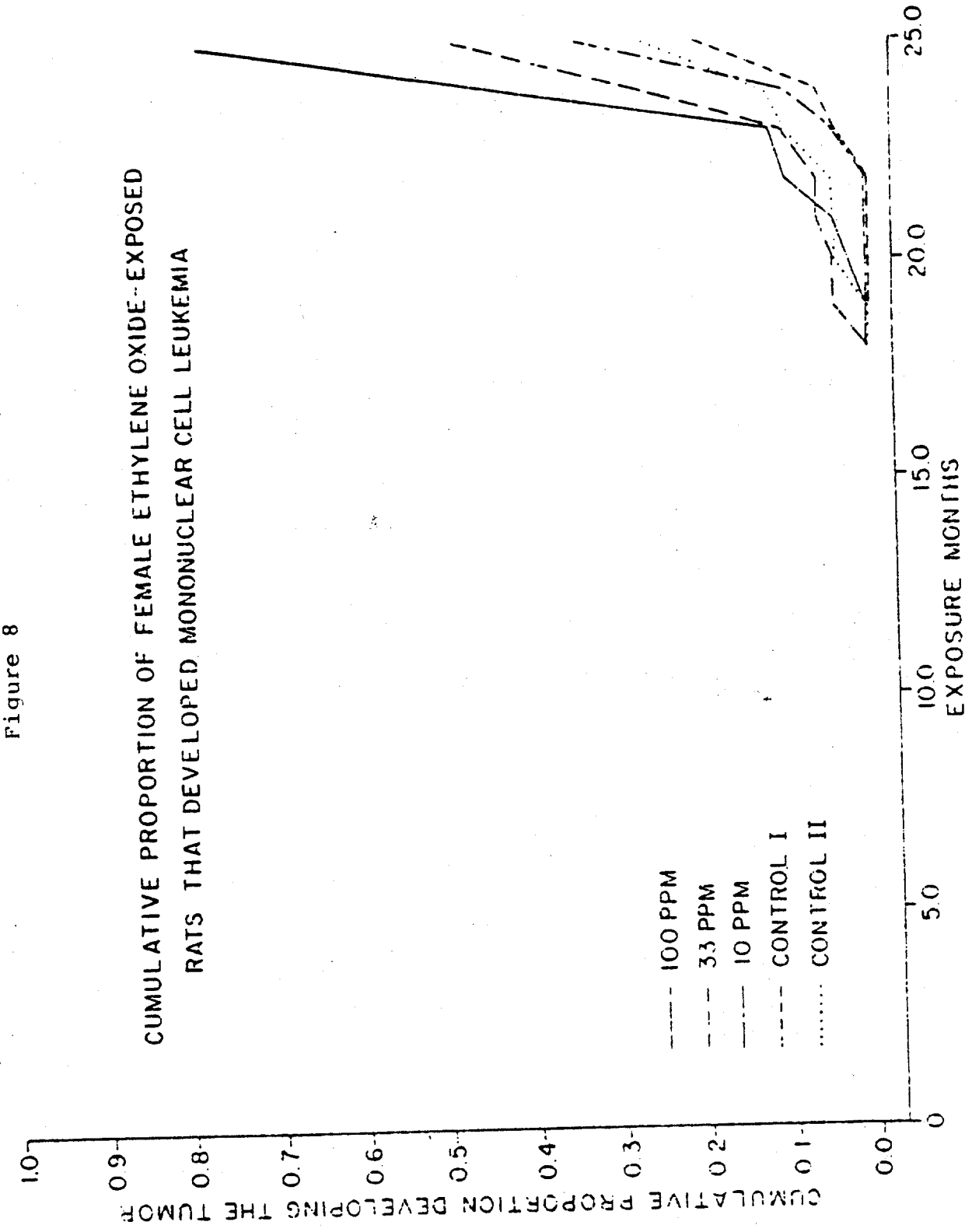

CUMULATIVE PROPORTION OF FEMALE ETHYLENE OXIDE-EXPOSED
RATS THAT DEVELOPED MONONUCLEAR CELL LEUKEMIA
CUMULATIVE PROPORTION DEVELOPING THE TUMOR
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
5.0
10.0
15.0
20.0
25.0
EXPOSURE MONTHS
100 PPM
33 PPM
10 PPM
CONTROL I
CONTROL II

Figure 9

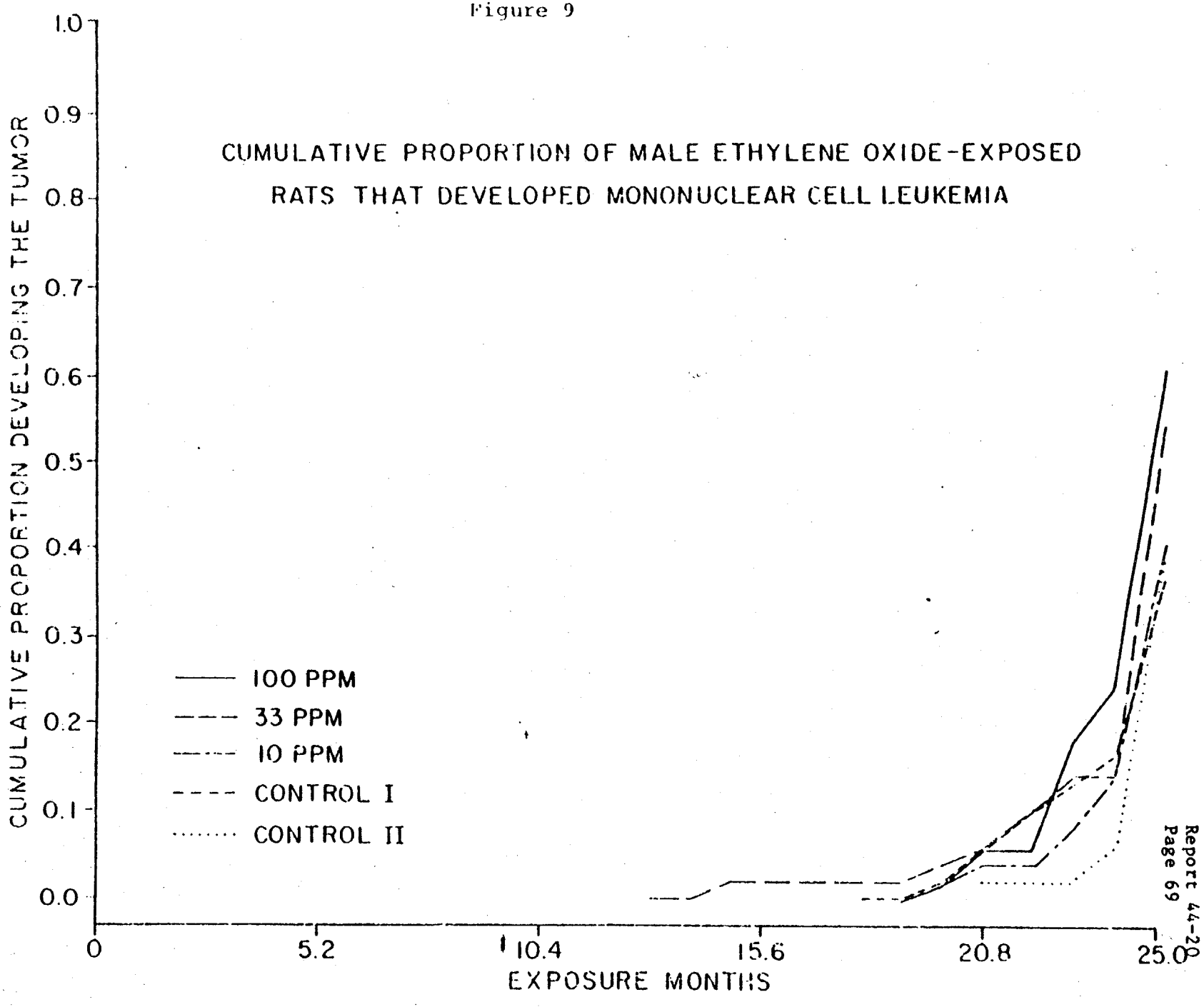
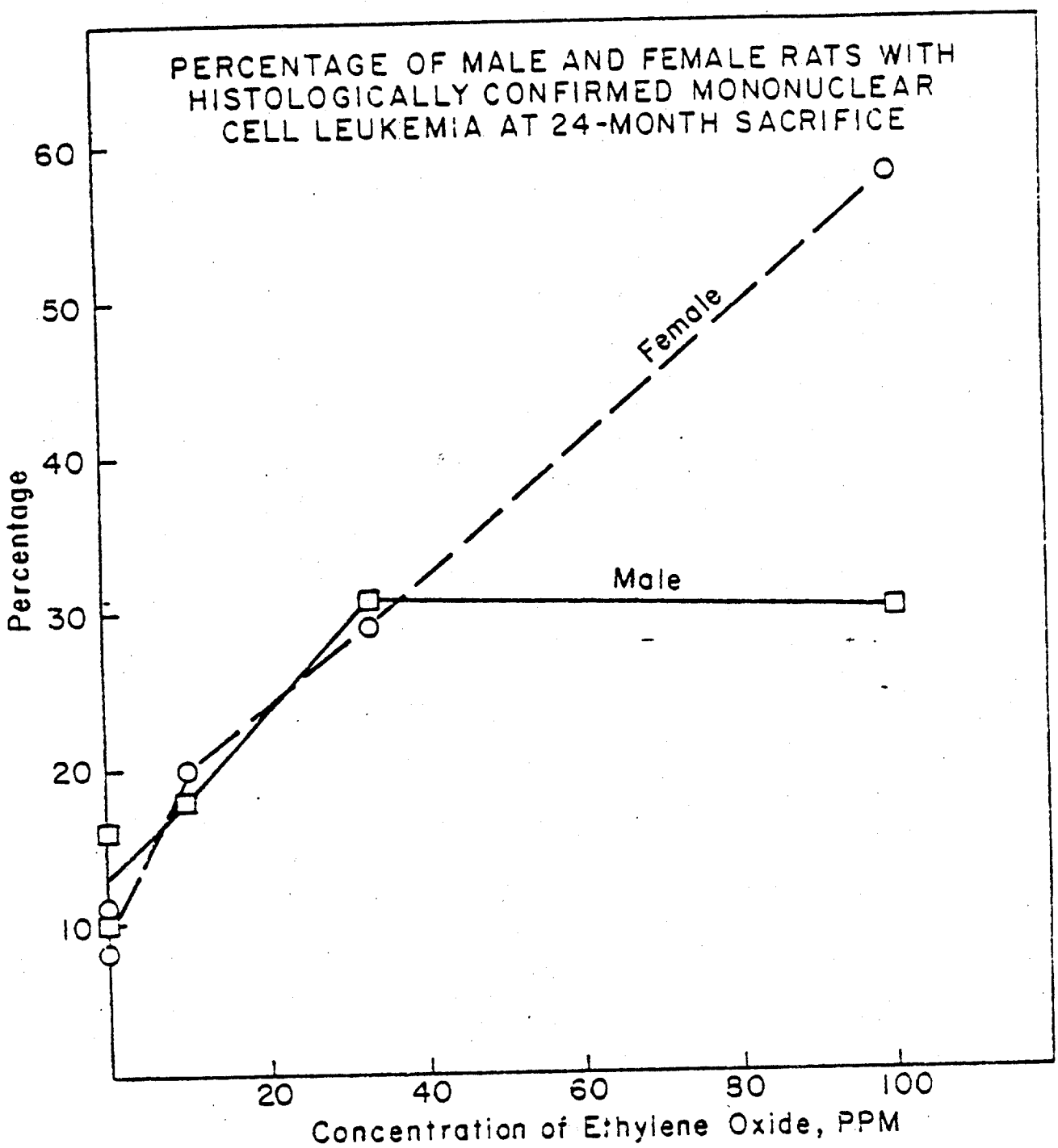

CUMULATIVE PROPORTION OF MALE ETHYLENE OXIDE-EXPOSED RATS THAT DEVELOPED MONONUCLEAR CELL LEUKEMIA
CUMULATIVE PROPORTION DEVELOPING THE TUMOR
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
100 PPM
33 PPM
10 PPM
CONTROL I
CONTROL II
0
5.2
10.4
15.6
20.8
25.0
EXPOSURE MONTHS

Figure 7-A


PERCENTAGE OF MALE AND FEMALE RATS WITH HISTOLOGICALLY CONFIRMED MONONUCLEAR CELL LEUKEMIA AT 24-MONTH SACRIFICE
Percentage
60
50
40
30
20
10
Female
Male
20
40
60
80
100
Concentration of Ethylene Oxide, PPM

trend noted for the EO-exposed females when the tumor proportions were not adjusted for early mortality ($p < 0.01$). The trend became even stronger ($p < 0.00001$) when the proportions were adjusted. These data suggest that exposure to EO not only increased the total incidence of this leukemia but also accelerated its rate of development.

Males, Peritoneal Mesothelioma: (Table A-74 and Figure 10). The first peritoneal mesothelioma was observed in the 100 ppm group approximately three months before a tumor of this type was noted in either control group; however, it is noted that the principle cause of death of this rat from the 100 ppm group was not mesothelioma. The median time to tumor was the 23rd exposure month for the 100 ppm group and the 25th month for the 33 ppm group. There was only a total of two peritoneal mesotheliomas for each air-control group; consequently, no median time to tumor was calculated for these groups. From the 21st exposure month until the termination of the study, the value of the cumulative percentage developing this tumor in the 100 ppm group was statistically significantly higher than those of both control groups. The cumulative percentage value of the 33 ppm group was not appreciably higher than those of the controls until the last month. The cumulative percentages of the rats having peritoneal mesothelioma at the termination of the study were 47, 22 and 8% for the 100 ppm, 33 ppm and 10 ppm groups, respectively, whereas the value for both control groups was 5%. At the 24-month sacrifice interval, similar treatment-related effects were observed. Moreover, the trend analysis results indicate an unequivocal relationship ($p < 0.0001$) between exposure to EO and the induction of peritoneal mesothelioma.

Males, Pituitary Adenoma: (Table A-75 and Figure 11). The first pituitary adenomas appeared at 15 months in the 100 and 33 ppm groups, whereas, the first tumor of this type did not appear until the 17th or 18th month in all other groups. The prevalence of this tumor observed both in the 100 ppm and in one of the control groups was not appreciably different throughout the study. However, the occurrence of a significant positive trend ($p < 0.01$) indicates that the normal prevalence of pituitary adenomas in the male rats was accelerated by exposure to ethylene oxide (as before in other trend analyses, assuming that the tumor caused the early death of the rats). At the final sacrifice interval, only the prevalence in the 100 ppm group was elevated (not statistically significant) in comparison to the other groups.

Females, Pituitary Adenoma: (Table A-76 and Figure 12). The first pituitary adenoma in the females was noted in the 100 ppm group at the 10th month, 5 months earlier than in either control group. At the 21st, 22nd and the 24th month, the 100 ppm group cumulative percentage incidence of this tumor was statistically significantly higher than those of one control or the combined controls. However, after including the relatively high incidences of pituitary adenomas for all groups at the final sacrifice interval, the final cumulative indexes were all almost identical. At no time was there a significant elevation in this tumor in the 33 ppm group.

The results of the trend analyses for pituitary adenomas for the female rats were similar to those for the males except that the probability was < 0.0001, highly significant.

Figure 10

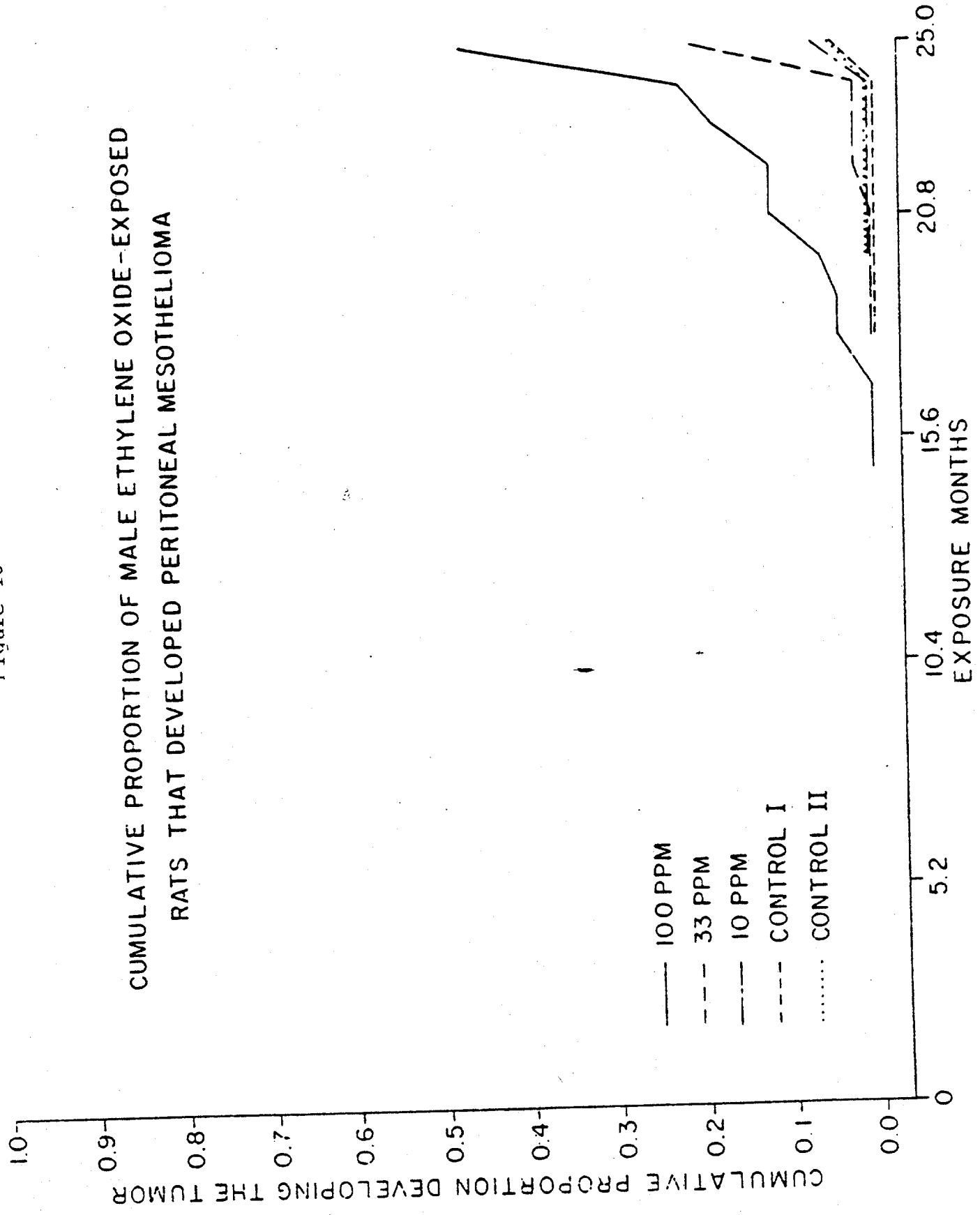

CUMULATIVE PROPORTION OF MALE ETHYLENE OXIDE-EXPOSED
RATS THAT DEVELOPED PERITONEAL MESOTHELIOMA
CUMULATIVE PROPORTION DEVELOPING THE TUMOR
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
5.2
10.4
15.6
20.8
25.0
EXPOSURE MONTHS
100 PPM
33 PPM
10 PPM
CONTROL I
CONTROL II

Figure 11

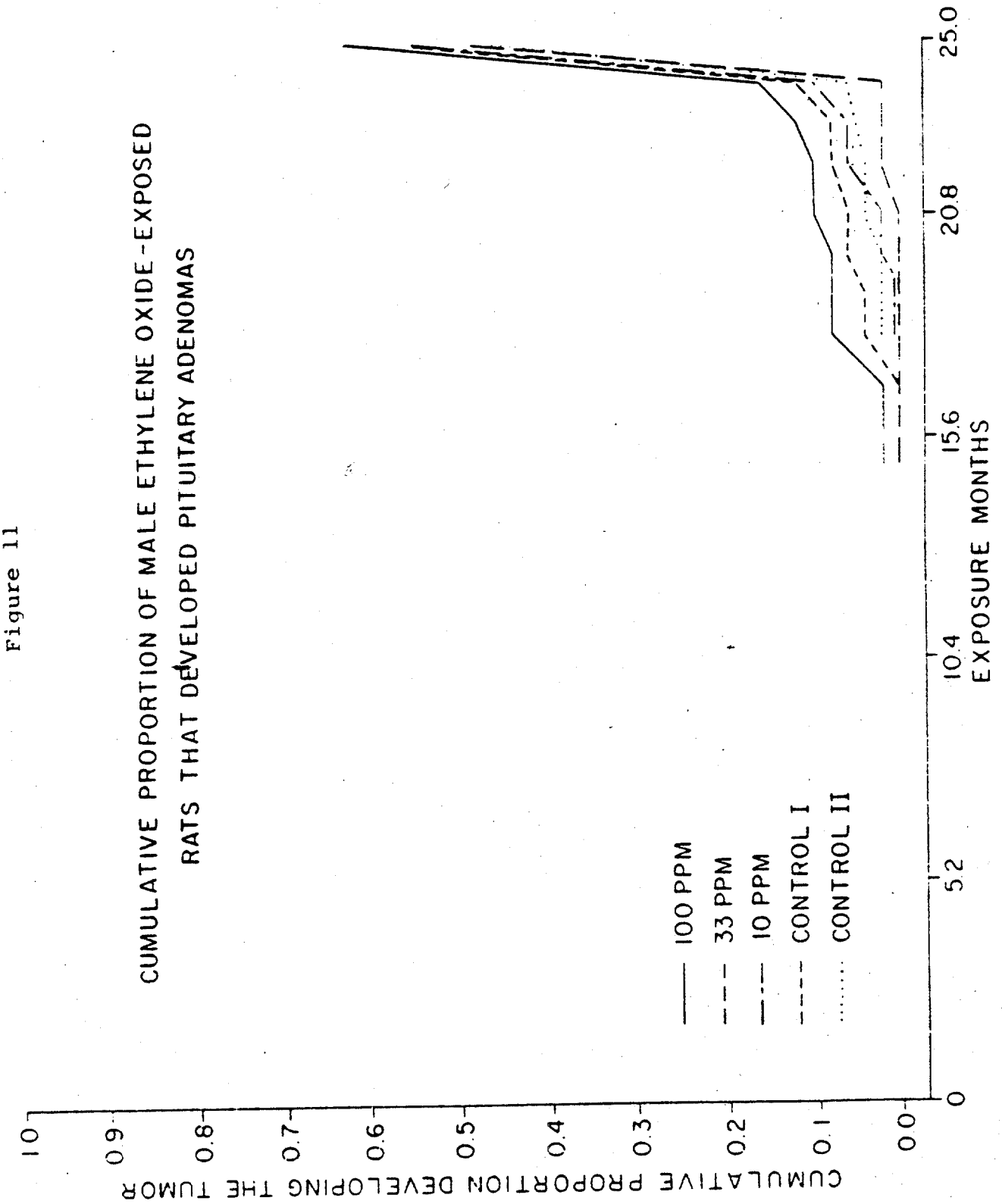
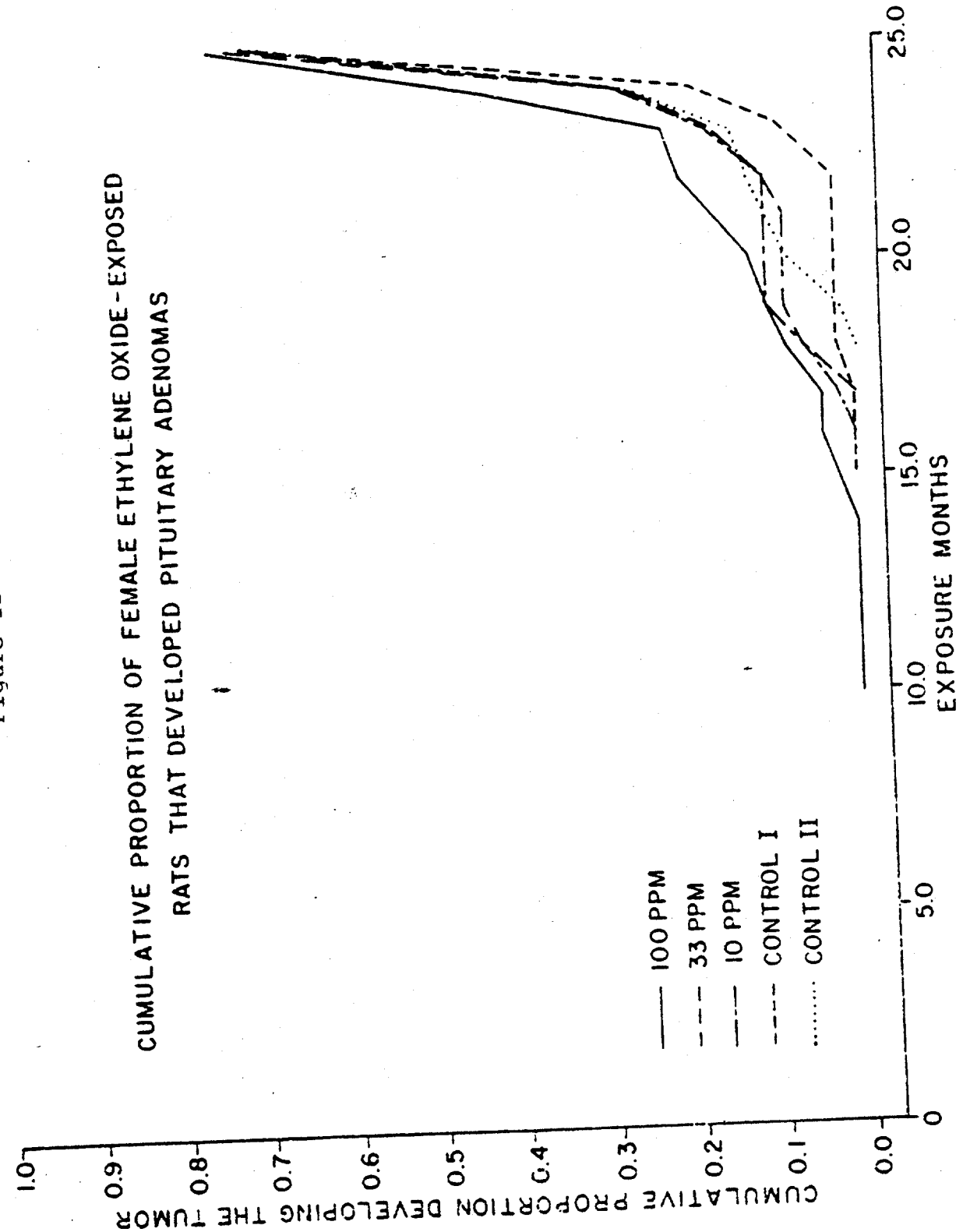

CUMULATIVE PROPORTION OF MALE ETHYLENE OXIDE-EXPOSED
RATS THAT DEVELOPED PITUITARY ADENOMAS
CUMULATIVE PROPORTION DEVELOPING THE TUMOR
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
0
5.2
10.4
15.6
20.8
25.0
EXPOSURE MONTHS
100 PPM
33 PPM
10 PPM
CONTROL I
CONTROL II

Figure 12


CUMULATIVE PROPORTION OF FEMALE ETHYLENE OXIDE-EXPOSED
RATS THAT DEVELOPED PITUITARY ADENOMAS
CUMULATIVE PROPORTION DEVELOPING THE TUMOR
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
5.0
10.0
15.0
20.0
25.0
EXPOSURE MONTHS
100 PPM
33 PPM
10 PPM
CONTROL I
CONTROL II

Incidental Tumors: There were no statistically significant differences (Table 37) in the frequency for any of the selected tumors classified as incidental including pituitary adenoma when the data were analyzed by the Gart method. The data for these selected tumors are presented as follows: adrenal pheochromocytoma, males -- Table A-77 and Figure 13; pancreas islet cell adenoma, males — Table A-78 and Figure 14; thyroid follicular adenoma, males — Table A-79 and Figure 15; testes interstitial cell tumor, males -- Table A-80 and Figure 16.

Consequentially, any differences in frequency noted in comparison to controls of these tumor types are not considered to be related to treatment. However, it is noted that the cumulative percentage of rats with thyroid follicular adenoma in the males of the 100 ppm group was appreciably higher than any other group mainly because of the increased proportion (not statistically significant) of rats with this tumor found at the final sacrifice period.

Proportion of Animals with Neoplasms

The number of rats with a primary neoplasm(s) (one or more) and the number with a malignant neoplasm(s) (one or more) for each group is presented in Table 38 for moribund and dead rats and those killed at the 18- and 24-month sacrifice intervals. For the male rats, no significant differences were noted, and, at the 24-month sacrifice interval, the frequencies were similar for all treatment levels. In general, most of the rats (75% or more) from each group had at least one neoplasm. However, it was observed that there were more neoplasms per rat in the 100 ppm group at this sacrifice interval. The mean number of neoplasms per neoplasm-bearing rat was 4.2 for the 100 ppm group, whereas it was approximately 3.2 for all other groups (Appendix XII, Table 5). The statistical significance of this is noted in the analysis of the number of rats with 2 or more or 3 or more primary neoplasms. These values of the 100 ppm group were significantly higher than those of the controls, as indicated in Table 39. The number of males with malignant neoplasms was not affected by treatment (Table 39). (NOTE: It is recognized that tabulation of neoplasms and malignant neoplasms may be performed by the two different ways as indicated in Tables 39 and 40. It is our recommendation that primary neoplasms of the same type within one organ be tabulated separately and that a liver neoplastic nodule not be tabulated as a malignant neoplasm but as a neoplasm.)

For the female rats, no significant differences were observed for the number of rats with one or more primary neoplasms in the moribund and dead rats and in those killed at the 18- and 24-month sacrifice intervals. However, elevated values for the mean number of neoplasms per neoplasm-bearing rat were noted in the EO-treated animals. These values for the 100, 33 and 10 ppm groups were 2.2, 1.7 and 1.8, respectively, whereas for the controls they were 1.3 and 1.4. This is supported by the finding that the number of female rats in the 100 ppm group with 2 or more and 3 or more primary neoplasms was significantly higher than those of both controls (Table 40). Moreover, when the data of two control groups were combined (both groups were similar) and statistical comparisons were

Table 37

Ratios of Number of Rats with "Incidental" Tumors to Number at Risk [1] for Rats Exposed to Ethylene Oxide for Two Years

Condition	Concentration of Ethylene Oxide				
	100 ppm	33 ppm	10 ppm	Control I	Control II
Pituitary Adenoma (Females)	32/106(30)[2]	38/89(43)	39/90(43)	38/109(35)	38/106(36)
Pituitary Adenoma (Males)	27/93(29)	16/73(22)	27/78(35)	28/95(29)	22/96(23)
Adrenal Pheochromocytoma (Males)	22/107(21)	14/94(15)	16/100(16)	17/106(16)	19/105(18)
Pancreas Islet Cell Adenoma (Males)	10/59(17)	1/33(3)	3/23(13)	2/64(3)	8/65(12)
Thyroid Follicular Adenoma (Males)	6/52(11)	1/53(2)	2/65(3)	1/63(2)	2/66(3)
Testes Interstitial Cell Tumor (Males)	75/91(82)	71/82(87)	80/88(91)	86/94(91)	86/94(91)

[1] Number at risk = Number alive at the time the first tumor in any group was observed. No statistical significances noted for any "incidental" tumors (Statistical analysis method: Cart et al., J. Natl. Cancer Inst. 62, 961, 1979).

[2] Numbers in parentheses are percentages

Figure 13

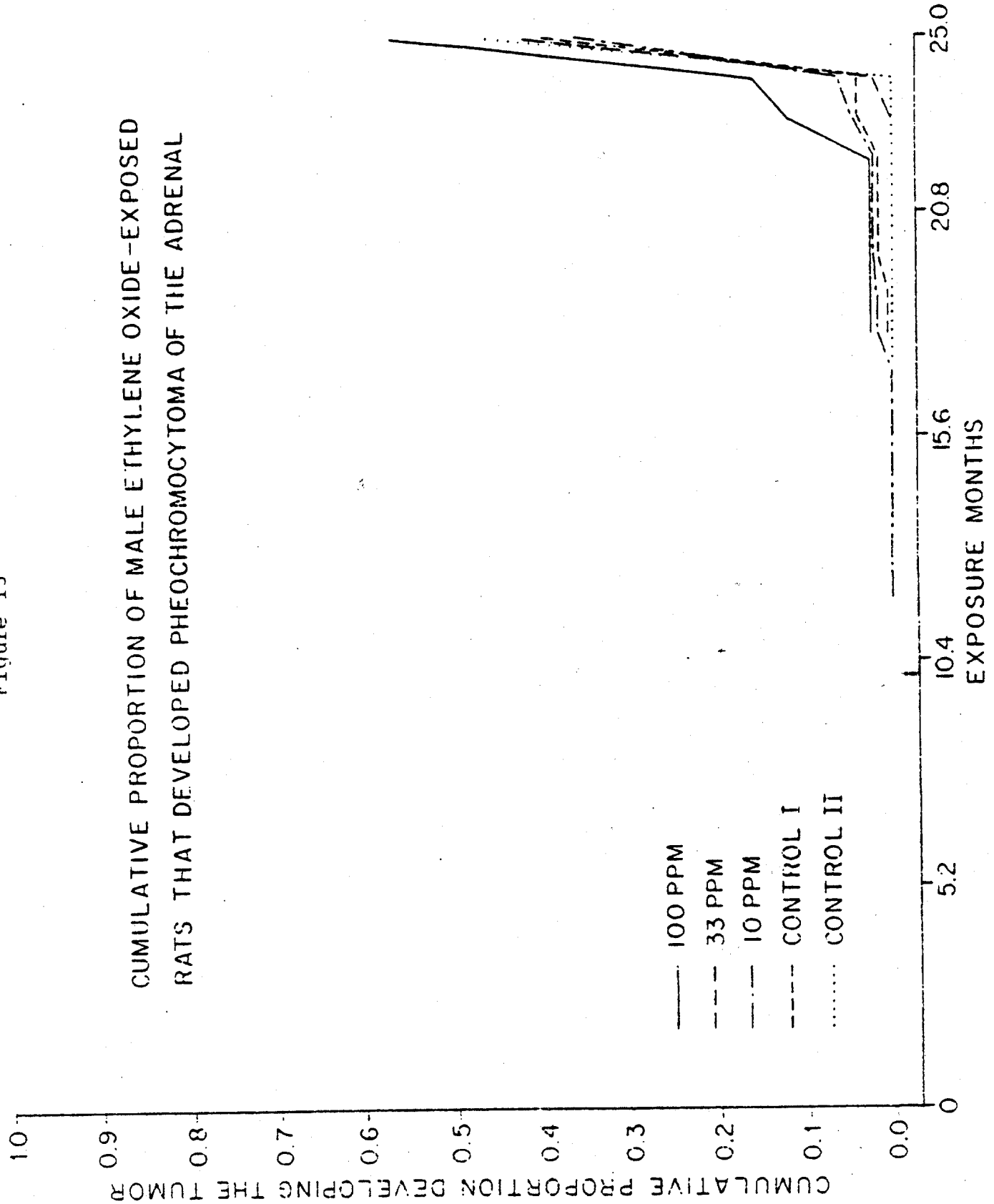

CUMULATIVE PROPORTION OF MALE ETHYLENE OXIDE-EXPOSED
RATS THAT DEVELOPED PHEOCHROMOCYTOMA OF THE ADRENAL
CUMULATIVE PROPORTION DEVELOPING THE TUMOR
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
5.2
10.4
15.6
20.8
25.0
EXPOSURE MONTHS
100 PPM
33 PPM
10 PPM
CONTROL I
CONTROL II

Figure 14

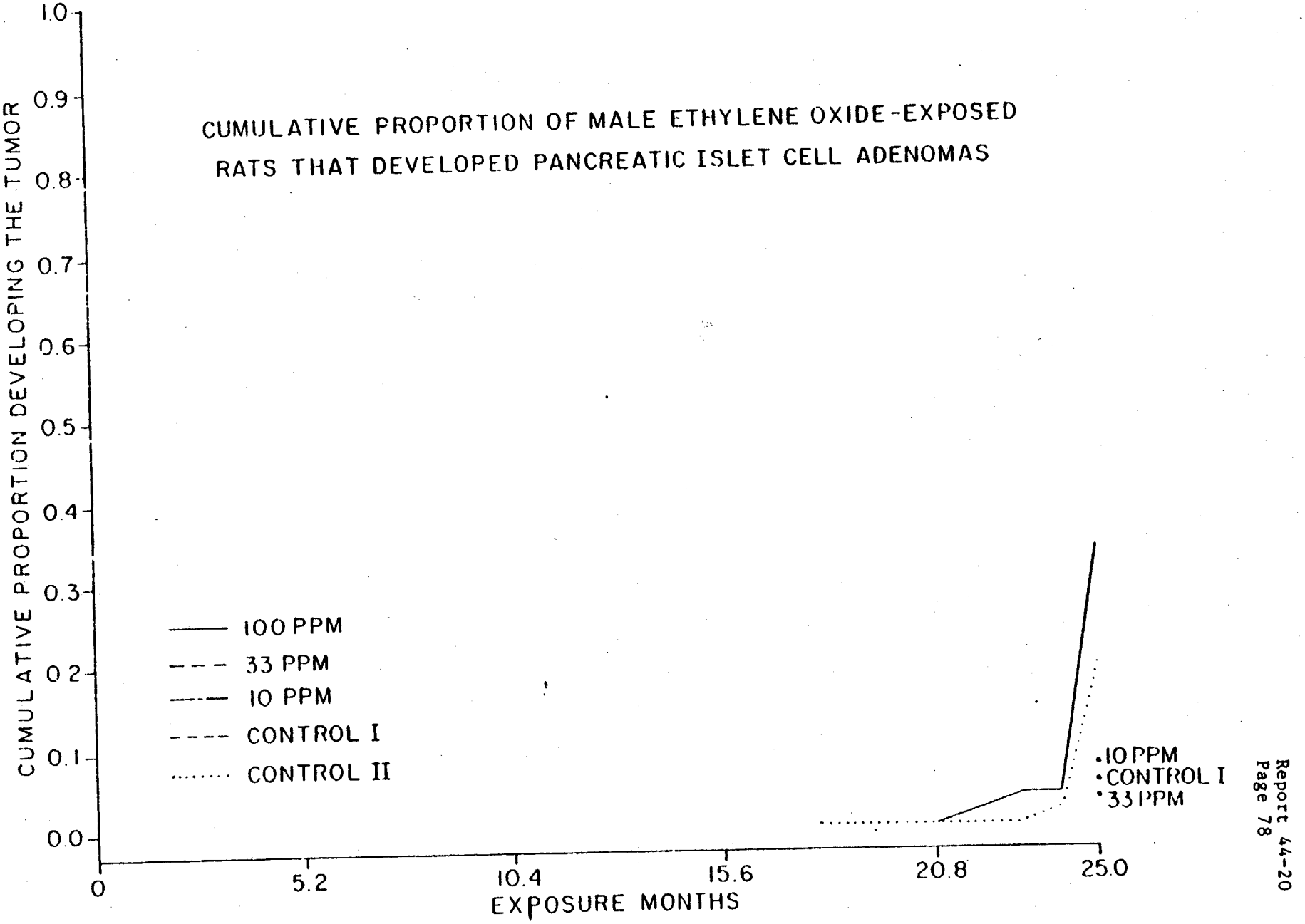
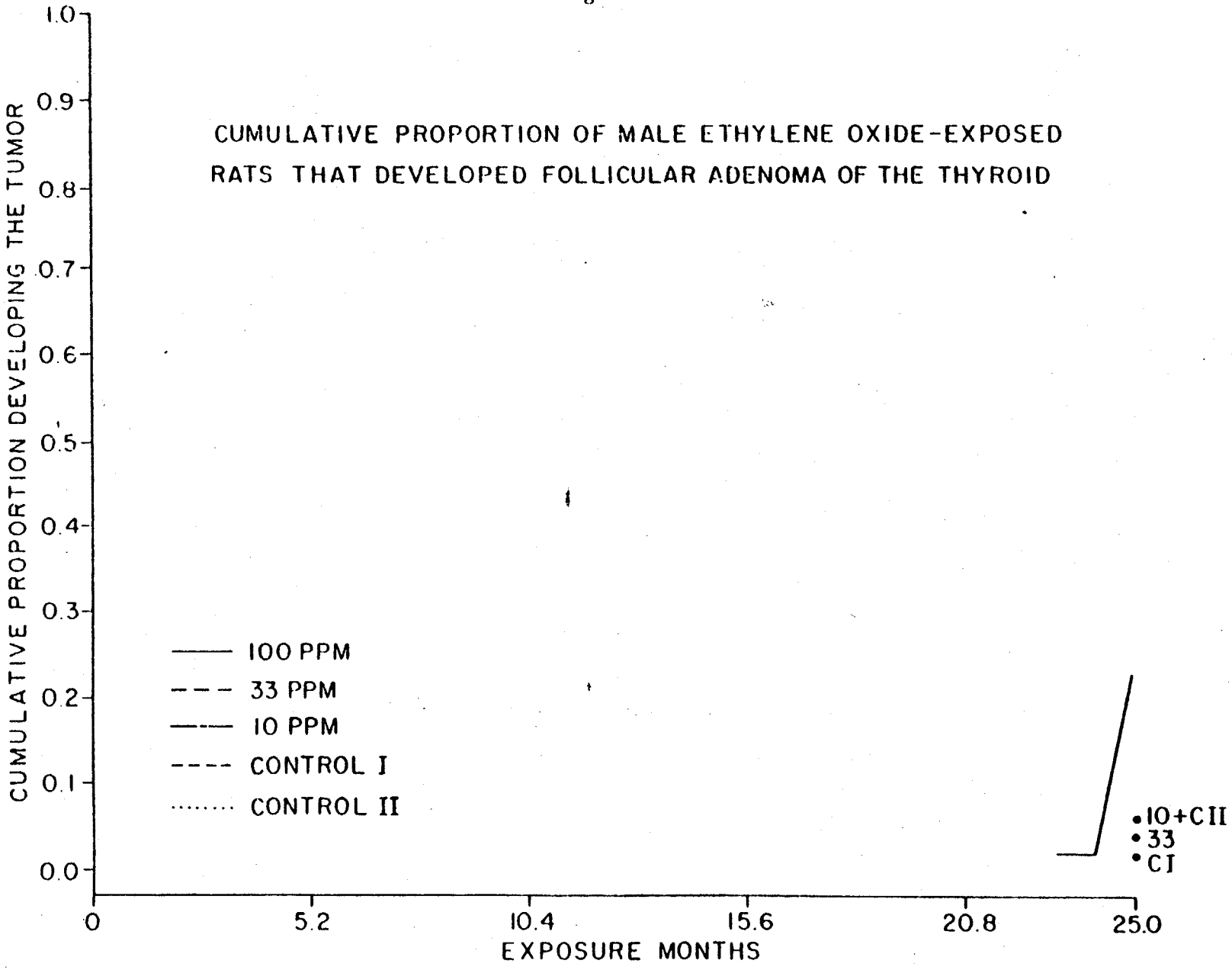

CUMULATIVE PROPORTION OF MALE ETHYLENE OXIDE-EXPOSED RATS THAT DEVELOPED PANCREATIC ISLET CELL ADENOMAS
CUMULATIVE PROPORTION DEVELOPING THE TUMOR
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
100 PPM
33 PPM
10 PPM
CONTROL I
CONTROL II
10 PPM
CONTROL I
33 PPM
0
5.2
10.4
15.6
20.8
25.0
EXPOSURE MONTHS

Figure 15


CUMULATIVE PROPORTION OF MALE ETHYLENE OXIDE-EXPOSED RATS THAT DEVELOPED FOLLICULAR ADENOMA OF THE THYROID
CUMULATIVE PROPORTION DEVELOPING THE TUMOR
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
100 PPM
33 PPM
10 PPM
CONTROL I
CONTROL II
•10+CII
•33
•CI
0
5.2
10.4
15.6
20.8
25.0
EXPOSURE MONTHS

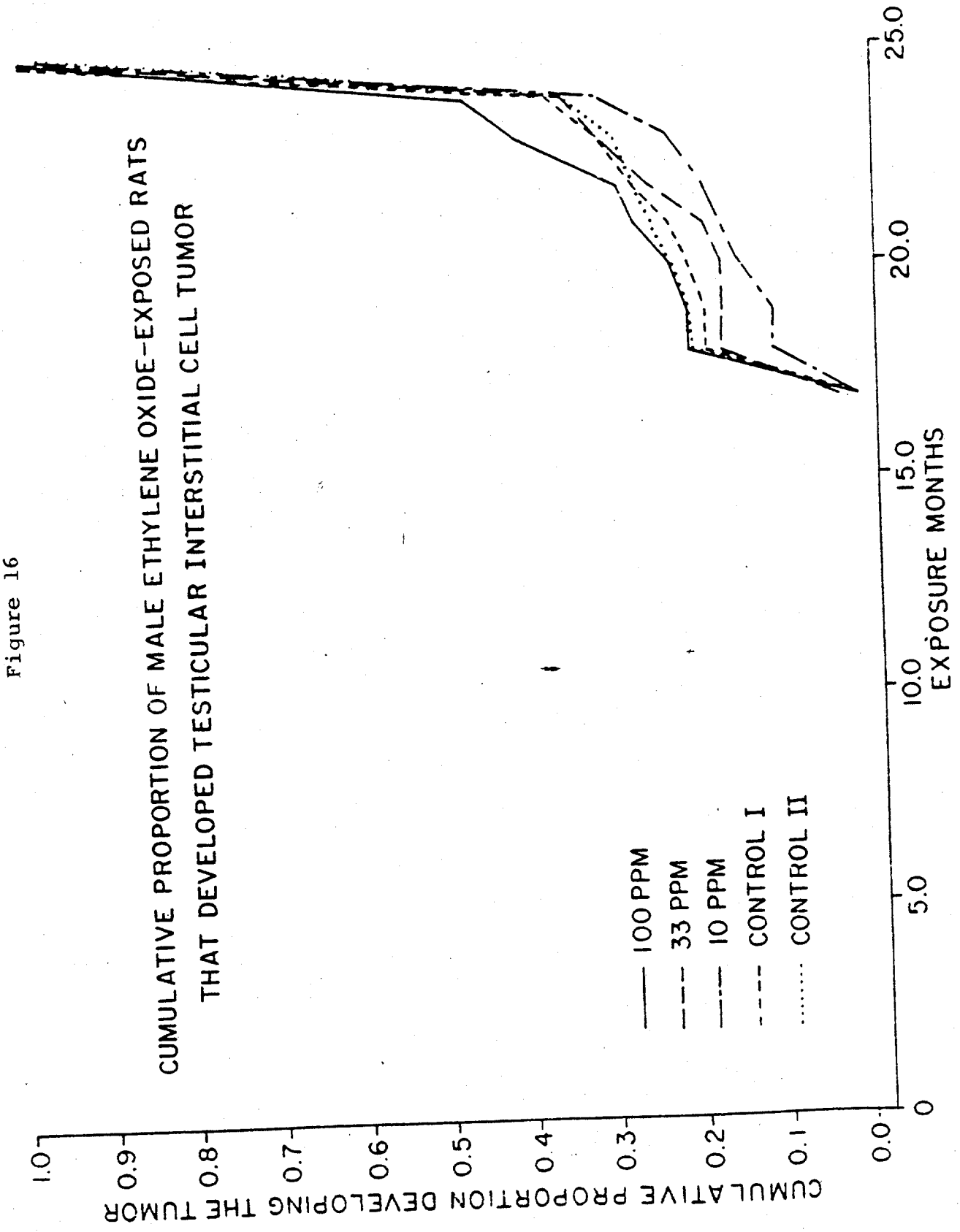

CUMULATIVE PROPORTION OF MALE ETHYLENE OXIDE-EXPOSED RATS
THAT DEVELOPED TESTICULAR INTERSTITIAL CELL TUMOR
CUMULATIVE PROPORTION DEVELOPING THE TUMOR
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
5.0
10.0
15.0
20.0
25.0
EXPOSURE MONTHS
100 PPM
33 PPM
10 PPM
CONTROL I
CONTROL II

Figure 16

Table 38

Number of Rats with Primary Neoplasms*: Two-Year Ethylene Oxide (EO) Study

Exposure Level, ppm	Moribund and Dead Rats[1] Number of Rats Examined	No. of Rats (%) with Neoplasm	No. of Rats (%) with Malignancy	18-Month Sacrifice[1] Number of Rats Examined	No. of Rats (%) with Neoplasm	No. of Rats (%) with Malignancy	24-Month Sacrifice[1] Number of Rats Examined	No. of Rats (%) with Neoplasm	No. of Rats (%) with Malignancy	24-Month Sacrifice[2] Number of Rats Examined	No. of Rats (%) with Neoplasm	No. of Rats (%) with Malignancy
Males												
100	49	41 (84)	33 (67)	20	11 (55)	4 (20)	30	27 (90)	12 (40)	30	27 (90)	12 (40)
33	40	30 (75)	23 (58)	20[3]	1 (5)	1 (5)	39[4]	30 (77)	19 (49)	39[4]	30 (77)	21 (54)
10	28	25 (89)	17 (61)	20[3]	3 (15)	1 (5)	51[4]	38 (75)	18 (35)	51[4]	38 (75)	18 (35)
C-I	30	24 (80)	19 (63)	20	6 (30)	2 (10)	48	37 (77)	12 (25)	48	37 (77)	14 (29)
C-II	29	24 (83)	17 (59)	20	4 (20)	1 (5)	49	39 (80)	15 (31)	49	39 (80)	19 (39)
CI + CII**	59	48 (81)	36 (61)	40	10 (25)	3 (8)	97	76 (78)	27 (28)	97	76 (78)	32 (33)
Females												
100	53	35 (66)	19 (36)	20	13 (65)	2 (10)	26	24 (92)	15 (58)$^{(c,a,c)}$	26	24 (92)	17 (65)$^{(c,b,c)}$
33	31	28 (90)	14 (45)	20[3]	6 (30)	0 (0)	48	39 (81)	17 (35)$^{(a,-,a)}$	48	39 (81)	17 (35)$^{(b,-,a)}$
10	24	20 (83)	8 (33)	20[3]	6 (30)	0 (0)	54	44 (81)	17 (31)	54	44 (81)	20 (37)$^{(b,-,a)}$
C-I	19	16 (84)	6 (32)	20	9 (45)	0 (0)	60	48 (80)	6 (10)	60	48 (80)	6 (10)
C-II	20	17 (85)	9 (45)	20	5 (25)	0 (0)	56	44 (79)	12 (21)	56	44 (79)	13 (23)
CI + CII**	39	33 (85)	15 (38)	40	14 (35)	0 (0)	116	92 (79)	18 (16)	116	92 (79)	19 (16)

a = $0.05 > p > 0.01$ b = $0.01 > p > 0.001$ c = $p < 0.001$

*Testicular interstitial cell tumors are excluded from this tabulation, but all other histologically confirmed neoplasms are included.
**Control groups C-I and C-II are combined.

[1]Liver neoplastic nodule not tabulated as a malignancy.
[2]Liver neoplastic nodule tabulated as a malignancy.
[3]Only gross lesions were examined in the 18-month 33 and 10 ppm groups.
[4]For certain organs or tissues, e.g., mammary gland, only gross lesions were examined at 33 and at 10 ppm. If all other tissues had been examined these incidences or percentages could have been higher than reported.

First letter of superscript denotes significance vs. Air Control I; second letter of superscript denotes significance vs. Air Control II and third letter denotes degree of significance vs. combined control groups (C-I plus C-II). Bracketed superscripts denote values significantly higher than those of control groups.

Table 39

Frequency of Primary Neoplasms[1]

In Male Rats Sacrificed after 24-Months of Exposure to Ethylene Oxide

	Exposure Concentration, ppm					Combined Controls
	100	33*	10*	0-I	0-II	0-I & 0-II
No. of Males	30	39	51	48	49	97
Primary Neoplasms of the Same Type Within One Organ Tabulated as One						
	Primary Neoplasms; Number (Percentage)					
One or more	27(90)	30(77)	38(75)	37(77)	39(80)	76(78)
Two or more	21(70)$^{(a,a,a)}$	19(49)	21(41)	18(38)	19(39)	37(38)
Three or more	14(47)$^{(b,a,c)}$	7(18)	5(10)	5(10)	7(14)	12(12)
Primary Neoplasms of the Same Type Within One Organ Tabulated Separately[2]						
	Primary Neoplasms; Number (Percentage)					
Two or more	21(70)$^{(-,-,a)}$	19(49)	22(43)	18(38)	20(41)	38(39)
Three or more	14(47)$^{(a,a,b)}$	9(23)	7(14)	6(12)	8(16)	14(14)
Four or more	6(20)	3(8)	1(2)	1(2)	4(8)	5(5)
Five or more	3(10)	2(5)	1(2)	0(0)	1(2)	1(1)
Liver Neoplastic Nodule Not Tabulated as a Malignancy						
	Primary Malignaucy; Number (Percentage)					
One or more[3]	12(40)	20(51)	17(33)	13(27)	16(33)	29(30)
Two or more	2(7)	2(5)	2(4)	0(0)	1(2)	1(1)
Liver Neoplastic Nodule Tabulated as a Malignancy						
	Primary Malignancy; Number (Percentage)					
One or more[3]	12(40)	21(54)	18(35)	14(29)	19(39)	33(34)
Two or more	2(7)	3(8)	2(4)	0(0)	1(2)	1(1)

a = $0.05 > p > 0.01$ b = $0.01 > p > 0.001$ c = $p < 0.001$

First letter of superscript denotes degree of significance vs. Air Control I (0-I); second letter denotes degree of significance vs. Air Control II (0-II); third letter denotes degree of significance vs. combined control groups (0-I plus 0-II). Bracketed superscripts denote values significantly higher than those of control groups.

[1]Interstitial cell tumor of the testes not included in this tabulation, but all other histologically confirmed primary neoplasms are included.

[2]Exception to this tabulation procedure: Multiple tumors of the same type in the liver tabulated only once; mononuclear cell leukemia and peritoneal mesothelioma tabulated as one neoplasm each per rat.

[3]Only one rat (in 33 ppm) had more than two malignaucies; it had 3.

*For certain organs or tissues, e.g., mammary gland, only gross lesions were examined at 33 and at 10 ppm. If all other tissues had been examined, these incidences or percentages could have been higher than reported.

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Table 40

Frequency of Primary Neoplasms[1]

In Female Rats Sacrificed after 24-Months of Exposure to Ethylene Oxide

	Exposure Concentration, ppm					Combined Controls
	100	33*	10*	0-I	0-II	0-I & 0-II
No. of Females	26	48	54	60	56	116
Primary Neoplasms of the Same Type Within One Organ Tabulated as One						
	Primary Neoplasms; Number (Percentage)					
One or more	24(92)	39(81)	44(81)	48(80)	44(79)	92(79)
Two or more	16(62)$^{(b,b,c)}$	18(38)	23(43)$^{(-,-,a)}$	12(20)	11(20)	23(20)
Three or more	9(35)$^{(b,a,c)}$	6(12)	5(9)	2(3)	3(5)	5(4)
Primary Neoplasms of the Same Type Within One Organ Tabulated Separately[2]						
	Primary Neoplasms; Number (Percentage)					
Two or more	16(62)$^{(b,b,c)}$	19(40)$^{(-,-,a)}$	24(44)$^{(-,-,b)}$	12(20)	11(20)	23(20)
Three or more	10(38)$^{(c,b,c)}$	8(17)	7(13)	2(3)	3(5)	5(4)
Liver Neoplastic Nodule Not Tabulated as a Malignancy						
	Primary Malignancy; Number (Percentage)					
One or two[3]	15(58)$^{(c,a,c)}$	17(35)$^{(a,-,a)}$	17(31)	6(10)	12(21)	18(16)
Two	4(15)$^{(-,-,b)}$	2(4)	3(6)	0(0)	0(0)	0(0)
Liver Neoplastic Nodule Tabulated as a Malignancy						
	Primary Malignancy; Number (Percentage)					
One or two[3]	17(65)$^{(c,b,c)}$	17(35)$^{(b,-,a)}$	20(37)$^{(b,-,a)}$	6(10)	13(23)	19(16)
Two	4(15)$^{(-,-,a)}$	3(6)	4(7)	0(0)	1(2)	1(1)

a = $0.05 > p > 0.01$ b = $0.01 > p > 0.001$ c = $p < 0.001$

First letter of superscript denotes degree of significance vs. Air Control I (0-I); second letter denotes degree of significance vs. Air Control II (0-II); third letter denotes degree of significance vs. combined control groups (0-I plus 0-II). Bracketed superscripts denote values significantly higher than those of control groups.

[1]All histologically confirmed primary neoplasms are included.

[2]Exceptions to this tabulation procedure: Multiple tumors of the same type in the liver tabulated only once; mononuclear cell leukemia tabulated as one neoplasm per rat.

[3]No more than two malignancies in any rat.

*For certain organs or tissues, e.g., mammary gland, only gross lesions were examined at 33 and at 10 ppm. If all other tissues had been examined, these incidences or percentages could have been higher than reported.

Table 41
Type and Prevalence of Malignancies[1] in Male Rats
Sacrificed at 24 Months With and Without Mononuclear Cell Leukemia

	Exposure Concentration				
	100 ppm	33 ppm	10 ppm	0-I	0-II
Number of Rats Histologically Examined	30	39	51	48	49
Mononuclear Cell Leukemia (%)	9(30)	12(31)	9(18)	5(10)	8(16)
Prevalence of Male Rats with Mononuclear Cell Leukemia and Other "Malignancies"					
Skin, fibrosarcoma	1	-	-	-	-
Peritoneum, mesothelioma	1	-	1	-	-
Peritoneum, mesothelioma and salivary gland carcinoma	-	1	-	-	-
Preputial gland carcinoma	-	1	-	-	-
Subcutis, fibrosarcoma	-	-	1	-	-
Skeletal muscle, fibrosarcoma	-	-	-	-	1
Total number (percentage of rats with leukemia)	2 (22)	2 (17)	2 (22)	0 (0)	1 (12)
Prevalence of Other "Malignancies" in Male Rats Without Mononuclear Cell Leukemia					
Peritoneum, mesothelioma	3	3	1	1	1
Thyroid, follicular carcinoma	-	1	-	1	1
Thyroid, parafollicular cell carcinoma	-	-	4	-	2
Heart, neurofibrosarcoma	-	1	1	-	-
Jejunum, leiomyosarcoma	-	1	-	-	-
Ileum, leiomyosarcoma	-	1	-	-	-
Subcutis, fibrosarcoma	-	1	-	-	-
Preputial gland, squamous cell carcinoma	-	-	1	-	-
Liver, hepatocellular carcinoma	-	-	1	1	-
Liver, cholangiocarcinoma	-	-	-	1	-
Lung, squamous cell carcinoma	-	-	-	1	-
Eyes, neuroblastoma	-	-	-	1	-
Skin, squamous cell carcinoma	-	-	-	1	2
Skin, fibrosarcoma	-	-	-	1	-
Pituitary carcinoma	-	-	-	-	2
Total number (percentage of rats without leukemia)	3(14)	8(30)	8(19)	8(19)	8(20)

[1]Liver neoplastic nodule is not tabulated as a malignancy in this table. The same animal is not in more than one category.

Table 42

Type and Prevalence of Malignancies[1] in Female Rats

Sacrificed at 24 Months With and Without Mononuclear Cell Leukemia

	Exposure Concentration				
	100 ppm	33 ppm	10 ppm	0-I	0-II
Number of Rats Histologically Examined	26	48	54	60	56
Mononuclear Cell Leukemia (%)	15(58)	14(29)	11(20)	5(8)	6(11)
Prevalence of Female Rats With Mononuclear Cell Leukemia and Other "Malignancies"					
Lung, fibrosarcoma	1	-	-	-	-
Mammary gland, adenocarcinoma	2	1	1	-	-
Pinna, leiomyosarcoma	1	-	-	-	-
Skin, squamous cell carcinoma	-	1	-	-	-
Thyroid, follicular adenocarcinoma	-	-	1	-	-
Zymbal gland, squamous cell carcinoma	-	-	1	-	-
Total number (percentage of rats with leukemia)	4(27)	2(14)	3(27)	0(0)	0(0)
Prevalence of Other "Malignancies" in Female Rats Without Mononuclear Cell Leukemia					
Adrenal, cortical carcinoma	-	-	-	-	1
Mammary gland, adenocarcinoma	-	1	1	-	2
Nasal, squamous cell carcinoma	-	-	1	-	-
Pituitary, carcinoma	-	-	-	-	1
Tail, fibrosarcoma	-	-	-	1	-
Thyroid, follicular adenocarcinoma	-	1	-	-	1
parafollicular cell carcinoma	-	-	2	-	1
Uterus, carcinoma	-	-	1	-	-
leiomyosarcoma	-	1	-	-	-
squamous cell carcinoma	-	-	1	-	-
Total number (percentage of rats without leukemia)	0(0)	3(9)	6(14)	1(2)	6(12)

[1]Liver neoplastic nodule is not tabulated as a malignancy in this table. The same animal is not in more than one category.

WPC/1092-7

SUMMARY AND CONCLUSIONS

Prior to the final sacrifice, a depression in the rate of body weight gain and an increased mortality were the major effects noted in the groups of Fischer 344 rats exposed to 100 or 33 ppm of ethylene oxide by the inhalation route. At no time was there an effect noted for these parameters in the rats of the 10 ppm exposure group. Based on the body weight data, female rats were adversely affected earlier and at a lower exposure concentration level (33 ppm) than the male rats. During an outbreak of viral sialodacryoadenitis (SDA) in the 15th exposure month, more rats died in the 100 and 33 ppm groups than in the other groups; the mortality rate was greater in the female rats. Following clinical recovery from the SDA infection, an increased mortality occurred in both sexes of the 100 and 33 ppm groups. There was no histologic evidence linking the cause of death to the SDA virus infection.

Special studies were performed during the present two-year study to provide additional information for areas in which effects had previously been reported, primarily from acute studies. Embree and Hine (1975) observed an increase in several types of chromosomal aberrations in rat bone marrow cells after inhalation exposure to 250 ppm of EO for 7 hours per day for 3 days. In the present study, no treatment-related differences in chromosomal aberrations of bone marrow cells were noted in rats exposed to 100 ppm EO for 12 months. Hollingsworth, et al., (1956) reported eye irritation in acute inhalation exposures to lethal concentrations of EO. In the present study, no treatment-related ophthalmologic lesions were observed. Blood clotting time was evaluated in the present study because Reyniers, et al., (1964) reported that an increase in this parameter in mice was related to the use of EO-sterilized bedding material. However, no alteration in blood clotting time was observed through 18 months of exposure (which was the last evaluation interval for this parameter).

At the 6-, 12-, and 18-month sacrifice intervals, there were no consistent patterns of association of any alteration in urinalysis or hematology or serum clinical chemistry or organ weight with histologically confirmed organ damage. The only noteworthy result was a slight depression in erythrocyte count and hemoglobin value in the female rats of the 100 ppm exposure group. Since this effect occurred at both 12 and at 18 months and because hemoglobin values were depressed in the preliminary 8-week rat inhalation study, this finding appears to be a treatment-related effect. However, without supportive evidence, i.e., depression of hematopoiesis or increased destruction of red blood cells, the cause of this effect remains unknown. A few other isolated significant differences were observed in the clinical pathologic evaluation, but the toxicologic importance of these is also unknown.

Hollingsworth (1956) reported testicular atrophy in rats exposed to 200 ppm of EO for 196 days; however, for 12 months of exposure at 100 ppm in the present study, no histopathologic changes associated with treatment were noted in the testes. After this time period, because of the normally high prevalence of preneoplastic lesions in the testes of the Fischer 344 rat, no meaningful interpretation of the testicular organ weight and subtle histopathologic alterations are possible. Both Jacobson (1956) and Hollingsworth (1956) reported hind-limb weakness and muscular atrophy in rats exposed to approximately 400 ppm for 6 weeks. In the present study, the hind-limb lift reflex test was used in an attempt to evaluate this reported functional change.

While no functional changes were observed throughout the study, mild skeletal muscular atrophy (not neurogenic) was histologically confirmed after two years of exposure to 100 ppm of EO.

As early as 18 months, and also at the final sacrifice, exposure to EO was related to an increased prevalence of spontaneous, age-associated adrenal cortical fatty metamorphosis; however, the biological significance of this finding is not known. No other histologic lesions at any of the scheduled necropsy intervals were related to EO exposure except for the neoplastic lesions noted at the final sacrifice interval. No common cause was determined which would explain the treatment-related deaths for either sex except for an increased prevalence of "non-incidental" neoplasms. Based on histologic evaluation of the animals that died and animals that were sacrificed, it was established that the prevalence of two "non-incidental" malignant neoplasms, viz., mononuclear cell leukemia and peritoneal mesothelioma, were increased because of exposure to EO. At the final sacrifice interval, the prevalence of this leukemia in female rats was dosage related and increased for each of the three EO exposure concentrations. The type of leukemia was the unique mononuclear cell leukemia characteristic of Fischer-344 rats (Davey and Moloney, 1970; Moloney et al., 1970) and not one of the lymphoid leukemias common in other strains and stocks of rats. The prevalence of peritoneal mesothelioma was treatment related in only the 100 and 33 ppm male exposure groups. These peritoneal neoplasms originated on the testicular mesothelium and were confined to the abdominal cavity. This neoplasm in this location occurs spontaneously in low incidence in male Fischer 344 rats as well as in other rat strains and stocks (Gould, 1977; Berman and Rice, 1979). An increase in the cumulative percentage of pituitary adenoma was also noted in the females of the 100 ppm group beginning at the 21st exposure month. However, the cumulative percentage value for both controls increased to the approximate percentage level of the 100 ppm group by the end of the study. Therefore, since the time to the first tumor was much earlier in the 100 ppm female group, it is possible that this earlier significant difference indicated that the normal incidence of this neoplasm was accelerated by exposure to EO.

At the final sacrifice interval, the number of neoplasms per neoplasm-bearing rat was elevated, especially in the EO-treated female rats. This was also demonstrated by the fact that the frequencies among female rats with more than 2 neoplasms were significantly greater for all three exposure concentrations when compared to the combined controls. A significant increase in the number of rats with malignant neoplasms was noted in the females only. This effect was observed in the 100 and the 33 ppm exposure groups.

It is not known what influence the SDA virus infection had on the outcome of this study. However, based on mortality ratios, clinical pathology results and histologic findings, it does appear that the virus had little or no effect on the health status of the air control groups following the "recovery" period. Most importantly, the prevalences in the controls, at the final sacrifice interval, of mononuclear cell leukemia, peritoneal mesothelioma and pituitary adenoma were similar to those reported in the literature for the Fischer 344 rat (Goodman, et al., 1979). A comparison of the prevalence values for the combined air control groups of the present study (BRRC) to those compiled by Goodman et al., on nearly 1800 control rats, is as follows:

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TOXIC SUBSTANCES

MAR 30 1995

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Terry R. O'Bryan

Terry R. O'Bryan
Risk Analysis Branch

Enclosure 12105A

H

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Date sent to triage: MAY 10 1995

NON-CAP (CAP)

Submission number: 12105 A

TSCA Inventory: (Y) N D

Study type (circle appropriate):

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ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

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STOX (CTOX) EPI RTOX GTOX

STOX/ONCO (CTOX/ONCO) IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

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CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ-0992-12105 SEQ: A

TYPE: (INT.) SUPP FLWP

SUBMITTER NAME: Rohm and Haas Company

SUB. DATE: 08/21/92 OTS DATE: 09/08/92 CSRAD DATE: 01/30/95

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0599) REFER TO CHEMICAL SCREENING
(0678) CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKERS/OTHERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

CHEMICAL NAME: Ethylene Oxide

CAS# 75-21-8

BEST COPY AVAILABLE

INFORMATION TYPE:		P	F	C
0201	ONCO (HUMAN)	01	02	04
(0202)	ONCO (ANIMAL)	01	02	04
0203	CELL TRANS (IN VITRO)	01	02	04
0204	MUTA (IN VITRO)	01	02	04
0205	MUTA (IN VIVO)	01	02	04
0206	REPRO/TERATO (HUMAN)	01	02	04
0207	REPRO/TERATO (ANIMAL)	01	02	04
0208	NEURO (HUMAN)	01	02	04
0209	NEURO (ANIMAL)	01	02	04
0210	ACUTE TOX. (HUMAN)	01	02	04
0211	CHR. TOX. (HUMAN)	01	02	04
0212	ACUTE TOX. (ANIMAL)	01	02	04
0213	SUB ACUTE TOX (ANIMAL)	01	02	04
0214	SUB CHRONIC TOX (ANIMAL)	01	02	04
(0215)	CHRONIC TOX (ANIMAL)	01	02	04

INFORMATION TYPE:		P	F	C
0216	EPI/CLIN	01	02	04
0217	HUMAN EXPOS (PROD CONTAM)	01	02	04
0218	HUMAN EXPOS (ACCIDENTAL)	01	02	04
0219	HUMAN EXPOS (MONITORING)	01	02	04
0220	ECO/AQUA TOX	01	02	04
0221	ENV. OCCC/REL/FATE	01	02	04
0222	EMER INCI OF ENV CONTAM	01	02	04
0223	RESPONSE REQEST DELAY	01	02	04
0224	PROD/COMP/CHEM ID	01	02	04
0225	REPORTING RATIONALE	01	02	04
0226	CONFIDENTIAL	01	02	04
0227	ALLERG (HUMAN)	01	02	04
0228	ALLERG (ANIMAL)	01	02	04
0239	METAB/PHARMACO (ANIMAL)	01	02	04
0240	METAB/PHARMACO (HUMAN)	01	02	04

INFORMATION TYPE:		P	F	C
0241	IMMUNO (ANIMAL)	01	02	04
0242	IMMUNO (HUMAN)	01	02	04
(0243)	CHEM/PHYS PROP	01	02	04
0244	CLASTO (IN VITRO)	01	02	04
0245	CLASTO (ANIMAL)	01	02	04
0246	CLASTO (HUMAN)	01	02	04
0247	DNA DAM/REPAIR	01	02	04
0248	PROD/USE/PROC	01	02	04
0251	MSDS	01	02	04
0299	OTHER	01	02	04

Ctox

TRIAGE DATA: NON-CBI INVENTORY
(YES)
CAS SR NO
IN TRANSIT

ONGOING REVIEW
YES (DROP/REFER)
NO (CONTINUE)
REFER

SPECIES
RAT

TOXICOLOGICAL CONCERN:
LOW
MED
(HIGH)

USE:

PRODUCTION:

COMMENTS: Rats (Fischer) were exposed to ethylene oxide vapors via inhalation at 10, 33, 100 ppm for 2 years. Histologic findings confirmed hematologic evidence that exposure to EO resulted in increased prevalence of mononuclear cell leukemia. This leukemia was seen in the high concentrations tested. Skeletal muscle atrophy, degeneration of erythrocyte were seen at the high concentration.

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ-0992-12105 SEQ. A

TYPE: (INT. SUPP FLWP)

SUBMITTER NAME: Rohm and Haas Company

SUB. DATE: 08/21/92 OTS DATE: 09/08/92 CSRAD DATE: 01/30/95

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
(0678) CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKERS/OTHERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

CHEMICAL NAME:

CAS#
75-21-8

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
(0202)	ONCO (ANIMAL)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
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0208	NEURO (HUMAN)	01 02 04
0209	NEURO (ANIMAL)	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
0212	ACUTE TOX. (ANIMAL)	01 02 04
0213	SUB ACUTE TOX (ANIMAL)	01 02 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
(0215)	CHRONIC TOX (ANIMAL)	01 02 04

INFORMATION TYPE:		P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
0224	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
0228	ALLERG (ANIMAL)	01 02 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
(0243)	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
0248	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

Onco

TRIAGE DATA:	NON-CBI INVENTORY	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN:	USE:	PRODUCTION:
	(YES)	YES (DROP/REFER)	RAT	LOW		
CAS SR	NO	NO (CONTINUE)		MED		
	DETERMINE	REFER		(HIGH)		

COMMENTS

0 0 0
> <ID NUMBER>
8(e)-12105A

> <TOX CONCERN>
H

> <COMMENT>
A TWO YEAR ONCOGENICITY STUDY IN RATS IS OF HIGH CONCERN. ANIMALS (120/SEX/GROUP) WERE EXPOSED VIA INHALATION TO 10 PPM, 33 PPM, OR 100 PPM TEST MATERIAL FOR 6 HOURS/DAY, 5 DAYS/WEEK. THERE WERE TWO CONTROL GROUPS EXPOSED SIMILARLY TO AIR ONLY. EXPOSED ANIMALS SHOWED INCREASED INCIDENCE OF MONONUCLEAR CELL LEUKEMIA, WITH A DOSE-DEPENDENT RESPONSE IN FEMALES. FEMALES AT ALL THREE LEVELS ALSO SHOWED AN INCREASE IN THE NUMBER OF ANIMALS WITH MORE THAN 2 NEOPLASMS. THE NUMBER OF FEMALES WITH MALIGNANT NEOPLASMS WAS INCREASED AT 33 PPM AND 100 PPM. THE FREQUENCY OF PERITONEAL MESOTHELIOMA WAS INCREASED IN MALES AT 33 PPM AND 100 PPM. THE TOTAL INCIDENCE OF PITUITARY ADENOMA WAS NOT INCREASED COMPARED TO CONTROLS, BUT THE ONSET OF PITUITARY ADENOMA WAS ACCELERATED IN HIGH DOSE FEMALES. STATISTICAL ANALYSIS IS INCLUDED IN THE SUBMISSION.

$$$$